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The Cost-Effectiveness of Cardiac Monitoring in Breast Cancer Patients Who Have Received Cardiotoxic Therapies

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by

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The Cost-Effectiveness of Cardiac Monitoring in Breast Cancer Patients Who Received Cardiotoxic Therapies

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The University of Texas at Austin, 2012

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It has been known that anthracycline-based chemotherapy has the potential to cause cardiac dysfunction in breast cancer patients; however, recently evidence has shown that the addition of trastuzumab increases this risk. The study objective was to compare the cost-effectiveness of monitoring for cardiotoxicity with B-type natriuretic peptide (BNP), multi-gated acquisition scanning (MUGA), echocardiography (ECHO) or no monitoring from a payer's prospective. Cost-effectiveness was compared between alternatives using an incremental cost-effectiveness ratio with outcomes of 1) quality-adjusted life-years and 2) percentage of patients diagnosed with each monitoring strategy. Costs estimates (in 2010 U.S. Dollars) of each strategy (obtained from the Center for Medicare and Medicaid Services website [www.cms.gov]) included the cost of the test, cost of treating heart failure once discovered (which includes medications, routine office visits, medication management) and the cost of potential acute care (which includes emergency department visits and hospitalizations). Estimates for the probabilities of heart failure development, disease progression, need for acute care, and mortality, as well as utility estimates for all disease stages were obtained from published literature. A 15-year time-frame was used with a 3% discount rate for both costs and QALYs.

In the base-case analysis, the average costs and QALYs for monitoring patients were $10,062/ 6.92 QALY, $13,627/4.22 QALY, $14,739/ 6.61 QALY and $15,656/ 6.49 QALY for BNP, No Monitoring, ECHO and MUGA respectively. When comparing all alternatives to BNP, the ICER values were negative, indicating that BNP was the dominant monitoring strategy. Percent detection was similar between the three monitoring methods [21-22 % for HER-2(-) and 30-31% for HER-2(+) patients]. Again BNP was dominant over the other monitoring strategies. Sensitivity analyses were robust to changes in discount rate, probability of patients testing HER-2 (+), probability of patients being diagnosed in an asymptomatic stage, incidence of cardiac dysfunction in patients receiving anthracycline therapy ± trastuzumab and estimate of disutility associated with additional testing. A probabilistic sensitivity analysis conducted via Monte Carlo simulation led to the same conclusion as the base-case analysis; BNP was the dominant strategy over all monitoring alternatives.

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Abbreviations

1. ACC: American College of Cardiology

2. ACE-I: Angiotensin-Converting-Enzyme Inhibitor

3. ACP: American College of Physicians

4. ACR: American College of Radiologists

5. ACS: Acute Coronary Syndromes

6. ACS: American Cancer Society

7. ADLs: Activities of Daily Living

8. AERS: Adverse Event Reporting System

9. AHA: American Heart Association

10. AMI: Acute Myocardial Infarction

11. AML: Acute Myelogenous Leukemia

12. APAP: Acetaminophen

13. ARB: Angiotensin Receptor Blocker

14. ASCO: American Society of Clinical Oncology

15. ASX: Asymptomatic

16. ATRA: All-Trans Retinoic Acid

17. AUC: Area Under the Curve

18. AWP: Average Wholesale Price

19. BCS: Breast Conserving Surgery

20. BID: Twice Daily

21. BI-RADS: Breast Imaging Reporting and Data System

22. BMI: Body Mass Index

23. BMT: Bone Marrow Transplant

24. BNP: B-Type Natriuretic Peptide

25. BSE: Breast Self-Exam

26. BUN: Blood Urea Nitrogen

27. CA: Cancer

28. CA: Conjoint Analysis

29. CABG: Coronary Artery Bypass Graft

30. CAD: Coronary Artery Disease

31. CBA: Cost-Benefit Analysis

32. CBC: Complete Blood Count

33. CBE: Clinical Breast Exam

34. CC: Complication/Comorbidity

35. CEA: Cost-Effectiveness Analysis

36. CER: Cost-Effectiveness Ratio

37. CHF: Congestive Heart Failure

38. CMA: Cost-Minimization Analysis

39. CMS: Center for Medicare and Medicaid Services

40. CNB: Core Needle Biopsy

41. COPD: Chronic Obstructive Pulmonary Disease

42. CPI: Consumer Price Index

43. CPT: Current Procedural Terminology

44. CR: Complete Response

45. CRP: C - Reactive Protein

46. CT: Computerized Tomography

47. CTC: Common Toxicity Criteria

48. CTCAE: Common Terminology Criteria for Reporting Adverse Events

49. CUA: Cost-Utility Analysis

50. CV: Contingent Valuation

51. DCE: Discrete Choice Experiment

52. DCIS: Ductal Carcinoma *in situ*

53. DES: Diethylstilbestrol

54. DOR: Diagnostic Odds-Ratio

55. DRG: Diagnosis-Related Group

56. DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

57. DVT: Deep Vein Thrombosis

58. DZR: Dexrazoxane

59. ECG: Electrocardiogram

60. ECHO: Echocardiogram

61. ECM: Extra-Cellular Matrix

62. ECOG: Eastern Cooperative Oncology Group

63. ED: Emergency Department

64. EDTA: Ethylene-Diamine-Tetra-Acetic Acid

65. EDV: End Diastolic Volume

66. EF: Ejection Fraction

67. ER: Estrogen Receptor

68. ESV: End Systolic Volume

69. FISH: Fluorescence *in situ* Hybridization

70. FN: False Negative

71. FNA: Fine Needle Aspirate

72. FP: False Positive

73. FS: Fractional Shortening

74. GAF: Global Assessment of Functioning

75. GI: Gastro-Intestinal

76. H/H: Hemoglobin/Hematocrit

77. HCPCS: Healthcare Common Procedure Coding System

78. HD: Heart Disease

79. HER-2: Human Epidermal Growth-Factor Receptor-2

80. HF: Heart Failure

81. HFSA: Heart Failure Society of America

82. HFSS: Heart Failure Survival Score

83. HRQoL: Health-Related Quality-of-Life

84. HRT: Hormone Replacement Therapy

85. HTN: Hypertension

86. HYE: Healthy-Year Equivalent

87. ICER: Incremental Cost-Effectiveness Ratio

88. ICU: Intensive Care Unit

89. IFN-α: Interferon Alpha

90. IHC: Immunohistochemical

91. IL-2: Interleukin-2

92. ISDN: Isosorbide Dinitrate

93. ITCs: Isolated Tumor Cells

94. JVD: Jugular Venous Distension

95. KPS: Karnofsky Performance Status

96. LCIS: Lobular Carcinoma *in situ*

97. LFT: Liver Function Test

98. LLN: Lower Limit of Normal

CHAPTER ONE: BACKGROUND

1.1 Introduction

Heart failure resulting from therapy is a relatively common adverse effect experienced in breast cancer patients. While true incidence and prevalence estimates are not known, published literature reports estimates that can range anywhere from 1 to 57%. The differences largely depend on the drug combination, degree of dysfunction reported, length of follow-up, and methods used for detection.

Treatment regimens vary in the amount of risk they confer, while use of an anthracycline agent alone is known to cause risk, combination with the targeted agent trastuzumab, is known to amplify that risk substantially. This poses somewhat of a dilemma in the treatment of patients. Anthracyclines, especially, doxorubicin, are a mainstay in breast cancer treatment and have been shown to have high activity against these tumors, essentially making breast cancer curable. Therefore, not administering anthracyclines because of the cardiac risk may diminish that patient's possibility of a cure. Trastuzumab is also extremely important in the treatment of breast cancer. Trastuzumab was specifically engineered to have activity in patients who over-express the HER-2 gene.

Although heart failure can be experienced by patients a number of years after therapy has been concluded, guidelines have yet to be developed that explicitly recommend a specific method or frequency to monitor cardiac function during routine surveillance. Patients can develop left ventricular dysfunction anytime during or after treatment, however, heart failure most commonly develops within the first year after the completion of chemotherapy.

In clinical trials, especially older trials, heart failure was not screened for unless the study participant had specific complaints suggestive of a heart failure diagnosis. This results in bias toward later stage (i.e. NYHA class III or IV) reporting. In more recent trials, where the risk of left ventricular dysfunction was known to be a possible effect, trial investigators screened patients using methods such as ECHO and MUGA scans.

A frequently encountered barrier to monitoring cardiac function is cost. Traditional methods to assess cardiac function include echocardiography (ECHO) and multi-gated acquisition scan (MUGA), both of which are costly and resource-intensive radiological procedures. Less invasive methods such as chest x-rays (CXR) and electrocardiograms (ECG) are significantly less costly; however, neither is sensitive nor specific enough to small changes in cardiac function to be useful for screening purposes. These factors make non-invasive, less expensive laboratory tests attractive alternatives for screening.

Numerous studies have evaluated the utility of B-type natriuretic peptide (BNP) levels in the heart failure setting and have concluded that BNP can adequately discriminate between patients with left ventricular dysfunction and those without. There have been additional studies examining the cost-effectiveness of BNP in patients presenting with acute symptoms and BNP was found to have saved resources when compared to other methods of screening.

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1.2 Overview

The purpose of this dissertation is to assess the cost-effectiveness of B-type natriuretic peptide monitoring in breast cancer patients receiving cardiotoxic therapies. To understand the importance of cost-effective strategies to screen for heart failure in breast cancer patients, one must understand the impact both disease states have on our society and the healthcare system. This requires knowledge of both breast cancer and heart failure disease processes, diagnoses, treatments and outcomes. Chapter one of this dissertation will give the necessary background regarding the diseases under investigation.

Chapters two and three will provide a review of the literature regarding cardiac dysfunction as a possible consequence of breast cancer therapy and possible strategies to detect potential cardiac dysfunction. Chapter two will provide a review of the literature regarding the cardiovascular consequences of breast cancer therapy. This will include a discussion of the mechanism of toxicity of various cancer therapies as well as the toxicity of specific agents and toxicity criteria. This chapter will also review the literature regarding heart failure in breast cancer patients. This discussion will include the incidence of dysfunction, risk factors, preventive strategies and management. This chapter will conclude with an overview of the outcomes and prognosis associated with therapy-induced cardiotoxicity as well as economic implications. Additionally, this chapter will provide evidence that will serve as data inputs for the Markov models that will be used to test the hypotheses under study. Chapter three will provide a review of the literature regarding detection of cardiovascular dysfunction in breast cancer patients. This will include the discussion of the various available methods, an overview of the

evidence for each testing procedure, comparison of available methods and the economic implications of various alternatives.

Chapter four will describe the methodology used for this dissertation. This chapter will provide details of the study methodology. This includes the purpose of the study and problem statement, study objectives with corresponding hypotheses to be tested. Additionally, this chapter gives an introduction to the economic evaluation in healthcare, types of analyses – with greater detail on cost-effectiveness analyses, as well as the use of decision analysis and Markov analyses. This chapter will also provide the specific estimates and parameters used for the model in this study as well as the sources of those estimates.

Chapter five will present the results for each of the study objectives with testable hypotheses, information on strategies under comparison, incidence of treatment-induced cardiac dysfunction, cost of monitoring, costs of outpatient heart failure treatment, and costs of acute care. The detailed results of cost-effectiveness analysis and sensitivity analyses are also included in this chapter. Chapter six includes a description of the study population, strategies under comparison and incidence of cardiac dysfunction. This chapter also includes a discussion of the base-case results, results of the sensitivity analyses, study limitations, study conclusions and possible directions for future research.

1.3 Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women in the United States accounting for an estimated 193,000 new cases and 40,000 deaths in 2009. [1] Age-specific incidence of breast cancer increases with age to a lifetime risk of one in eight or 12.67% (if living to 110 years of age); by age 40, approximately one in 250 women will be diagnosed with breast cancer annually, at age 60, the figure is one in 35. [2]

In the last decade, there has been a sharp decline in breast cancer incidence and disease-related mortality. The decrease in incidence has been attributed to the decreasing use of post-menopausal hormone replacement therapy, and the decrease in mortality has been attributed to improved treatments in the adjuvant and metastatic settings as well as the effects of early diagnosis through screening efforts. The five-year survival for all stages is approximately 89%; this improves to 98% for local disease. However, patients with regional lymph node involvement have a five-year survival of 83% and those with distant lymph node involvement approximately 26%. [3]

Due to therapy and earlier diagnosis, patients are seeing an increase in survival; however, there is also the possibility of experiencing delayed toxicities that do not present until after the treatment has concluded. Treatment-related toxicities happen relatively frequently in breast cancer, and the most common and deadly toxicity is chemotherapy-related heart failure.[4] Anthracyclines are a mainstay of breast cancer

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[1] N. Howlader et al., eds., "SEER Cancer Statistics Review 1975-2008" (Bethesda, Maryland: National Cancer Institute, 2011), http://seer.cancer.gov/csr/1975_2008/index.html.

[2] Ibid.; Rebecca Siegel et al., "Cancer Statistics, 2011," *CA: A Cancer Journal for Clinicians* 61, no. 4 (July 2011): 212–236.

[3] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

[4] Mohamed M. Haq et al., "Doxorubicin-induced Congestive Heart Failure in Adults," *Cancer* 56, no. 6 (1985): 1361–1365; Jan S. Moreb and David J. Oblon, "Outcome of Clinical Congestive Heart Failure Induced by Anthracycline Chemotherapy," *Cancer* 70, no. 11 (1992): 2637–2641.

therapy, however, their main limitation for use is the potential for cardiotoxicity; this potential increases substantially when use is combined with trastuzumab. [5]

The actual incidence of chemotherapy-related cardiotoxicity varies depending on the criteria used for reporting (e.g., any decline in left ventricular ejection fraction versus overt symptomatic heart failure) and how long patients are monitored for adverse effects (since patients can present with left ventricular dysfunction as many as 15 years after receiving an anthracycline). [6] There is an increasing number of breast cancer survivors resulting from improved therapy and screening; therefore, it has become apparent that a cost-effective mechanism for long-term monitoring of cardiotoxicity is needed after treatment is concluded. [7]

1.3.1 DISEASE PROCESS/EPIDEMIOLOGY

In the United States (U.S.) and worldwide, breast cancer is the most common type of cancer in women. In the U.S. breast cancer accounts for approximately 15% of cancer deaths (second to lung cancer), and is the main cause of death in women between the ages of 45-55. Worldwide, there are approximately one million new cases annually. The National Cancer Institute (NCI) estimates that approximately 12% of women will be diagnosed with breast cancer in their lifetime, and while improvements in early diagnosis

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[5] Moreb and Oblon, "Outcome of Clinical Congestive Heart Failure Induced by Anthracycline Chemotherapy."

[6] Dawn L Hershman et al., "Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma," *J Clin Oncol* 26, no. 19 (2008): 3159–3165; Robin L Jones, Charles Swanton, and Michael S Ewer, "Anthracycline Cardiotoxicity," *Expert Opinion on Drug Safety* 5, no. 6 (2006): 791–809.

[7] Michael R. Bristow et al., "Efficacy and Cost of Cardiac Monitoring in Patients Receiving Doxorubicin," *Cancer* 50, no. 1 (1982): 32–41; M.J. Horner et al., "SEER Cancer Statistics Review 1975-2006," *Surveillance Epidemiology and End Results*, 2010, http://seer.cancer.gov/csr/1975_2006/index.html.

and treatment have decreased mortality over the last decade, there are still approximately 40,000 deaths each year attributed to breast cancer. [8] In the U.S., approximately 200,000 women are diagnosed annually; this represents 26% of cancer diagnoses. While the incidence of breast cancer in the U.S. had been increasing steadily, partially due to an increase in use of mammographic screening, the number of new cases has recently stabilized and is beginning to decline. Despite this recent decline in the US, the incidence in the rest of the world is expected to continue to increase. From 2002-2006, the median age of diagnosis was 61, with no new cases under the age of 20. The SEER age-adjusted incidence rate was 123.8 cases per 100,000 women annually. [9]

1.3.2 RISK FACTORS

There are a number of risk factors that have been associated with breast cancer. These include both modifiable lifestyle risk factors and hereditary or genetic factors. [10] Prominent risk factors include age, race/ethnicity, diet, alcohol intake, weight and exogenous hormone use. Table 1.1 lists known risk factors for breast cancer, the relative risk (RR) for that risk factor as well as the definition for the "high-risk" group.

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[8] Horner et al., "SEER Cancer Statistics Review 1975-2006."

[9] Ibid.

[10] J. L Kelsey and G. S Berkowitz, "Breast Cancer Epidemiology," *Cancer Research* 48, no. 20 (1988): 5615; T. J Key, P. K Verkasalo, and E. Banks, "Epidemiology of Breast Cancer," *The Lancet Oncology* 2, no. 3 (2001): 133–140; K McPherson, C. M. Steel, and J. M. Dixon, "ABC of Breast Diseases: Breast Cancer---epidemiology, Risk Factors, and Genetics," *British Medical Journal* 321, no. 7261 (September 9, 2000): 624–628.

Table 1.1 Established and Probable Risk Factors for Breast Cancer[11]

Risk Factor	Relative Risk	High Risk Group
Age		
Advanced Age	> 10	Elderly
Age at menarche	3	Before age 11
Age at menopause	2	After age 54
Age at first full pregnancy	3	First child in early 40's
Family History		
First Degree Relative	≥ 2	Diagnosis at younger age
Previous benign disease	4 - 5	Atypical hyperplasia
Cancer in other breast	> 4	
Diet		
Saturated Fats	1.5	High intake
Alcohol	1.3	Excessive intake
Body Weight		
Premenopausal	0.7	BMI >35
Postmenopausal	2	BMI > 35
Exogenous Hormones		
OC's	1.24	Current use
HRT	1.35	Use over 10 years
DES	2	Use during pregnancy
Other		
Ionizing Radiation	3	Abnormal exposure in young females after age 10
Geographic Location	5	Developed countries

BMI: Body Mass Index, OC's: Oral Contraceptives, HRT: Hormone Replacement Therapy, DES: Diethyl Stilbestrol

[11] McPherson, Steel, and Dixon, "ABC of Breast Diseases."

Increasing age is the most prominent risk factor for breast cancer. The incidence of breast cancer rapidly increases during reproductive years and then slows down after the age of 50 or the onset of menopause. The cumulative incidence of breast cancer in the U.S. and Europe is approximately 2.7% by age 55, 5% by age 65 and 7.7% by age 65 (giving a doubling rate every 10 years). [12] Some countries see a flattening of the incidence-age curve after menopause because of the lack of hormone replacement therapy use seen abroad. [13]

In addition to age, there are racial differences in incidence for some groups. Non-Hispanic white women have the highest incidence of breast cancer worldwide which is peaks between the ages of 50-70. Non-Hispanic whites have a one-in-15 chance of developing breast cancer, compared to one-in-20 for African American women, one-in-26 in Asians or Pacific Islanders, and one-in-27 for Hispanics. Table 1.2 lists the breast cancer incidence rates by race as reported by SEER for calendar years 2002 to 2006. Mortality, however, is much higher in African Americans and Hispanics, which is commonly attributed to presentation at a more advanced stage. Hispanic and African American women are also more likely to be estrogen receptor (ER) negative, have a poorly differentiated disease and be diagnosed at an earlier age (commonly prior to menopause). The P53 mutation is more common in African American women but less common in Hispanic women when compared to non-Hispanic white women. [14]

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[12] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer"; McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[13] McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[14] Vinay Kumar et al., "Carcinoma of the Breast," in *Kumar: Robbins and Cotran Pathologic Basis of Disease*, 8th ed. (Saunders Elsevier, 2009), http://www.mdconsult.com.ezproxy.lib.utexas.edu/.

Table 1.2 Breast Cancer Incidence Rates by Race for 2002 – 2006 [15]

Race/Ethnicity	Rates[*] in Females
All	123.8
White	127.8
Black	117.7
Asian/Pacific Islander	89.5
American Indian/Alaska Native	74.4
Hispanic	88.3

[*]Rates are incidence per 100,000 women

Rates of breast cancer are highest in developed countries and lowest in non-developed countries and Japan (however, rates in Japan are increasing), with up to a five-fold difference worldwide in both incidence and mortality. Breast cancer rates in the U.S. and Western Europe are between four and seven times higher than the rest of the world with the risk in U.S. immigrants increasing with each generation (i.e., the immigrant risk is expected to be that of the host country within one to two generations). This is attributed to many modifiable risk factors (i.e., timing of childbirth, diet, exercise). [16]

There are several dietary factors that have been associated with breast cancer. Evidence supports a positive association between alcohol intake and diagnosis of breast cancer. There is equally strong evidence that an increase in folic acid intake is protective against breast cancer. There are a number of older studies that suggest an increase in fat intake is associated with the development of breast cancer; however, this is no longer believed to be true. It has been suggested that an increased BMI is a risk factor for breast cancer; this could be due to an increase in the amount of endogenous estrogen in women

[15] Horner et al., "SEER Cancer Statistics Review 1975-2006."
[16] Kumar et al., "Carcinoma of the Breast."

with an increased BMI. There is some evidence suggesting that intake of phytoestrogens or soy products may have a slight protective effect. [17]

Past medical history can also increase risk of developing breast cancer. Patients with a prior history of benign breast disease are at increased risk of developing subsequent breast cancer. Benign breast disease is divided into two types, proliferative and non-proliferative disorders. Non-proliferative breast disease does not confer a higher risk of breast cancer, whereas proliferative can increase risk two- to four-fold. [18] Patients with increased breast density on mammographic examination have a higher risk of developing breast cancer. [19] High breast density tends to cluster in families, is associated with both younger age and with hormone exposure. [20] It is suspected that high breast density is a result of incomplete or less complete involution of lobules at the end of each menstrual cycle, which may hypothetically increase the number of cells that are susceptible to neoplastic changes. [21] Breast density may be slightly modifiable in that hormone therapy appears to increase it whereas tamoxifen decreases density. Increased breast density also makes it more difficult to detect changes via mammography, which complicates the diagnosis. [22]

Radiation exposure as a risk factor for breast cancer was mainly based on studies of women exposed to atomic bomb radiation in World War II and studies of those who

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[17] Kelsey and Berkowitz, "Breast Cancer Epidemiology"; Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer"; McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[18] L. C Hartmann et al., "Benign Breast Disease and the Risk of Breast Cancer," *New England Journal of Medicine* 353, no. 3 (2005): 229; Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[19] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[20] G. A Colditz et al., "Family History, Age, and Risk of Breast Cancer: Prospective Data from the Nurses' Health Study," *Jama* 270, no. 3 (1993): 338.

[21] Kumar et al., "Carcinoma of the Breast."

[22] Ibid.

received therapeutic or diagnostic radiation. [23] Since levels of radiation received either therapeutically or during a diagnostic procedure are relatively low, it is extremely rare for these exposures to cause DNA mutations, and while radiation exposure is considered to be carcinogenic, it is extremely rare. It is estimated that about 1% of cases can be attributed to diagnostic radiology. [24] Those women under the age of 20 that receive radiation directly to the chest are theoretically at a higher risk than those women who are over the age of 50 or postmenopausal. [25]

There is an association between breast cancer and the number of ovarian cycles. The number of cycles depends on a number of things, including age at first menarche, age at onset of menopause , age at time of first full term child, or not having children. The younger the age at first menarche increases the number of cycles and increases risk, as does an older age at the onset of menopause and having no children. [26] However, the younger age at time of first full term pregnancy confers a lower risk of breast cancer, and the risk continues to decrease with an increasing number of full term pregnancies. [27] The effect of abortions (either spontaneous or induced) or miscarriages on breast cancer risk is not known. [28] There is evidence that a number of circulating hormones can increase risk of breast cancer. These include serum levels of estradiol, insulin-like growth factor-1 (pre-menopause) and prolactin (pre- or post-menopause). [29]

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[23] Kelsey and Berkowitz, "Breast Cancer Epidemiology"; McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[24] Martin Abeloff et al., "Cancer of the Breast," in *Abeloff: Abeloff's Clinical Oncology* (Philadelphia: Churchill Livingstone/Elsevier, 2008), Chapter 95, http://www.mdconsult.com.ezproxy.lib.utexas.edu/; Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[25] Abeloff et al., "Cancer of the Breast"; Kumar et al., "Carcinoma of the Breast."

[26] Abeloff et al., "Cancer of the Breast."

[27] Kumar et al., "Carcinoma of the Breast."

[28] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[29] Abeloff et al., "Cancer of the Breast"; Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

There have been many studies examining the use of exogenous hormones and their association with breast cancer. There is little evidence suggesting there is an association between oral contraceptive use and increased cancer risk. [30] Some studies suggest there may be an increase risk in current users of oral contraceptives (OC); however, since the incidence is extremely low in that age group, there are not many cases attributed to oral contraceptive use. Any additional risk from OC's declines rapidly after cessation of use and disappears after ten years. [31]

There is a demonstrated increase in risk of breast cancer in women who take hormone replacement therapy (HRT); however, the risk is only slightly increased with a RR of 1.023 per year of use. [32] In fact, the use of HRT for ten years is estimated to increase risk of breast cancer by about 35%. [33] Those women who are actively using hormone replacement therapy are at an increased risk compared to those who have never used them, and like oral contraceptives, the risk declines after cessation of use and any increased risk disappears five years after HRT has been stopped. [34] There are additional factors that may add to the risk associated with HRT. Combination HRT appears to confer greater breast cancer risk than using estrogen alone, and heavier women appear to have a lower risk than lean women who use HRT. [35]

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[30] Kumar et al., "Carcinoma of the Breast."

[31] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer"; McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[32] McPherson, Steel, and Dixon, "ABC of Breast Diseases."

[33] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[34] Zaid Abassi et al., "Implications of the Natriuretic Peptide System in the Pathogenesis of Heart Failure: Diagnostic and Therapeutic Importance," *Pharmacology & Therapeutics* 102, no. 3 (June 2004): 223–241.

[35] Katrina Armstrong, Andrea Eisen, and Barbara Weber, "Assessing the Risk of Breast Cancer," *The New England Journal of Medicine* 342, no. 8 (February 24, 2000): 564–571; Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

There are a number of older studies demonstrating an association between diethylstilbestrol (DES) and breast cancer. The estimated RR is approximately 1.5 and has been shown to be dose dependent; however today, the use of DES in pregnancy is banned. There have been some small studies that have suggested a potential increase in risk in women who have been exposed to fertility treatment; however, this association has not been confirmed in large populations. [36]

Family history is associated with approximately 10% of breast cancer diagnoses. Women with a first degree relative with breast cancer have an approximately two-fold increase in risk of developing breast cancer than those without a positive family history.[37] There are a number of genetic factors that are known to be associated with increased risk and that play a role at each stage of tumor development. [38] The most well established genes known to convey increased risk are the low prevalence genes BRCA1 and BRCA2. These genes account for approximately 2-3% of all cancers and 15-20% of familial cancers. Genetic testing for these alterations is now routinely performed in women who are considered high risk. Other genes that are definitively responsible for breast cancer have yet to be identified, and the processes involved in developing disease are not completely understood. [39]

There are a number of risk prediction tools available that combine risk factors and assign risk categories to women. These categories allow for a more efficient use of screening and preventive therapies. The breast cancer risk assessment tool (BCRAT) or Gail Model is a calculator-type tool. Table 1.3 lists the risk factors that the Gail Model

[36] Key, Verkasalo, and Banks, "Epidemiology of Breast Cancer."

[37] Colditz et al., "Family History, Age, and Risk of Breast Cancer."

[38] Richard Wooster and Barbara Weber, "Breast and Ovarian Cancer," *New England Journal of Medicine* 348, no. 23 (June 5, 2003): 2339–47.

[39] Ibid.

considers when calculating patient risk. There are separate calculators for blacks (African Americans) and non-Hispanic whites. The Gail model appears to be a good predictor of breast cancer; however, it has poor discrimination at the individual level. There is another program called BRCAPRO®, which can assess the probability of developing breast cancer in individuals with a strong family history. [40] The calculation tool is available at the National Cancer Institute website: http://www.nci.nih.gov/.

Table 1.3 Factors Used to Assess Risk in Modified Gail Model [41]

Item	Risk Factors Assessed	Effect on Risk†
1	Current Age	Increases With Age
2	Age at First Menarche	Increases if < 12
3	Age at first Live Birth	*
4	Number of First Degree Relatives With BC	*
5	Previous Benign Breast Biopsies	Increases†
6	Atypical Hyperplasia in Previous Breast Biopsy	Increases
7	Race/ Ethnicity	Formula varies by race

†Effect on risk determined by item response; *Responses to items 3 and 4 are combined to determine effect on risk; †the need for biopsy indicates histological change which increases risk; BC: Breast Cancer

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[40] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011," Professional Organization, *The National Comprehensive Cancer Network*, November 19, 2010, www.nccn.org.
[41] Ibid.

1.3.3 RISK-REDUCTION STRATEGIES

The American Cancer Society (ACS) has developed dietary guidelines for cancer prevention that include eating five or more servings of fruits/vegetables per day, eating whole grains instead of refined grains, limiting consumption of processed or red meats, and limiting alcohol consumption to ≤ one alcoholic beverage per day. Calcium and vitamin D may confer a slight protective effect if consumed from low-fat or fat-free dairy products or supplements. Consumption of soy products may also confer a slight protective effect. Additionally, exercise for 45 - 60 minutes per day on five or more days per week, which is designed to promote a healthy weight, can decrease circulating endogenous estrogen and consequently may provide a slight protective effect. [42]

In addition to diet and exercise recommendations that the ACS makes for all women; those at high risk should consider alternatives to exogenous hormones. Pre-menopausal women should consider using alternatives to oral contraceptives and consider having children earlier; post-menopausal women should forgo hormone replacement therapy and use other symptomatic treatment if possible. [43]

Raloxifene and tamoxifen are both approved for use in women at high risk of developing breast cancer. These drugs are selective estrogen receptor modulators and essentially block estrogen in some tissues. Aromatase inhibitors are being studied for protection in high risk women. Aromatase inhibitors are typically used in postmenopausal women with hormone receptor positive breast cancer and are not yet approved for use in preventive strategies. [44]

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[42] NCCN Breast Cancer Risk Reduction Panel Members, "Breast Cancer Risk Reduction V3.2011," Professional Organization, *National Comprehensive Cancer Network*, September 8, 2011, www.nccn.org.
[43] Ibid.
[44] Ibid.

1.3.4 SCREENING

Early stage disease is rarely symptomatic and is usually painless. Typically, early disease is discovered by noticing a hard lump warranting further examination by a health care professional. Lumps may make the breast appear asymmetric; however, often times there are no symptoms associated with early disease, and the disease can only be detected with more advanced screening methods such as mammography. [45] Screening methods include: breast self-exam, clinical breast exam, screen film mammography, digital mammography, computer aided detection, ultrasound and MRI. There are a number of factors that have to be considered when assessing the accuracy of screening methods and these factors include: availability of prior studies, body habitus, ethnicity, breast density, menstruating (changes in breast density due to cycle), and post-menopausal hormone therapy and breast surgery. [46]

It is estimated that about one-third of women in the U.S. perform regular breast self-exams with an estimated sensitivity between 20-30%. Although studies have shown that monthly self-exams do not affect mortality rates, and in fact, increase the number of biopsies performed due to false positives, many organizations still recommend that they be performed. [47] A Cochrane review of two large population studies (n = 388,535) compared self-exam to no intervention and found no difference in mortality between the groups. There were twice as many biopsies with benign results in the screening group than in the control group. There was an additional study included that compared self-exam to clinical examination, and due to poor follow- up, no conclusions could be made.

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[45] Abeloff et al., "Cancer of the Breast."

[46] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

[47] Michael S. O'Malley and Suzanne W. Fletcher, "Screening for Breast Cancer With Breast Self-examination," *JAMA: The Journal of the American Medical Association* 257, no. 16 (April 24, 1987): 2196–2203.

The authors of the Cochrane review concluded that more harm was added due to screening. [48]

In randomized controlled trials examining screening methods, the sensitivity of clinical breast exam is estimated at 54% (95% CI: 48 - 60%), and specificity is 94% (95% CI: 90 - 97%). Screening at the community level is unlikely to match that of a trial, and estimates for sensitivity in the community range from 28% - 36% for clinical breast exams. [49]

Breast cancers detected with screening mammography are typically smaller and have more favorable histological and biological features than those detected outside of screening. Since favorable prognostic outcomes attributed to mammography could be due to bias, trials that use mortality as the outcome of interest have become important to demonstrate any improvement that mammography provides. [50] A Cochrane review which included seven trials with a total of 600,000 patients who were randomized to mammographic screening versus no screening concluded that screening reduces mortality by 15%, but there is also an increase of 30% in over-diagnosis and unnecessary treatment. These authors also concluded that breast cancer mortality was an unreliable outcome in these trials and was biased in favor of screening because the cause of death was often misclassified. [51]

Seven population-based screening programs in the U.S. yielded an overall sensitivity of 75% and a specificity of 92.3%. These results are similar to those reported

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[48] Jan Peter Kösters and Peter C Gøtzsche, "Regular Self-examination or Clinical Examination for Early Detection of Breast Cancer," ed. The Cochrane Collaboration and Jan Peter Kösters, *Cochrane Database of Systematic Reviews*, no. 2 (2003), http://www2.cochrane.org/.

[49] J. G Elmore et al., "Screening for Breast Cancer," *Jama* 293, no. 10 (2005): 1245.

[50] Ibid.

[51] Peter C Gøtzsche and Margrethe Nielsen, "Screening for Breast Cancer with Mammography," ed. The Cochrane Collaboration and Peter C Gøtzsche, *Cochrane Database of Systematic Reviews*, no. 10 (2011), http://www2.cochrane.org/.

in numerous clinical trials examining screening mammography, yielding a sensitivity range of 68-88% and specificity range of 82-93%. Important predictors of accuracy are the age of the patient and breast density. [52]

Since the publication of the Cochrane review, many organizations still recommend using mammography as a screening tool; however, in many published recommendations, the age to initiate routine screening has changed. Additionally, since the publication of the review, all but one of the randomized screening trials excluded by the authors has been deemed to be methodologically sound by other reviewers. There are conflicting sets of guidelines regarding the use of screening mammography. The majority of North American groups recommend routine screening for "normal-risk" patients beginning at age 50; this includes the NCCN and ASCO.[53] The American College of Physicians (ACP) recommends that women in their 40s should consult with their physician to see if routine mammography is warranted, and The American Cancer Society recommends annual mammograms for women beginning at age 40. [54]

Although mammography is the most frequently utilized method for screening, there are an increasing number of studies reporting results using MRI as a screening tool for breast cancer. [55] A recent systematic review of 11 trials that compared MRI to mammography found that MRI had greater sensitivity than mammography (77% vs. 39%) but the specificity was found to be lower (86.3% vs. 94.7%). [56] Using a

[52] Elmore et al., "Screening for Breast Cancer."

[53] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

[54] Heidi D Nelson et al., "Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force," *Annals of Internal Medicine* 151, no. 10 (November 17, 2009): 727–737; Robert A Smith et al., "Cancer Screening in the United States, 2011," *CA: A Cancer Journal for Clinicians* 61, no. 1 (January 1, 2011): 8–30.

[55] Elmore et al., "Screening for Breast Cancer."

[56] Ellen Warner et al., "Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer," *Annals of Internal Medicine* 148, no. 9 (May 6, 2008): 671 –679.

combination is recommended by the ACS for women at very high risk as defined by risk prediction models, they also recommend against the use of MRI in women with a lifetime risk less than 15%. There are no clear recommendations for the use of MRI in women who rate a lifetime risk between very high (20-25%) and 15%. [57]

The National Comprehensive Cancer Network (NCCN) recommends the consideration of MRI use in high-risk women with the following circumstances [58]: Have a BRCA1 or BRCA2 mutation; Have a first-degree relative with a BRCA1 or BRCA2 mutation and they themselves are untested; Have a lifetime risk of 20-25% or more as defined by models largely dependent on family history; Received radiation therapy to the chest between the ages of 10 and 30 for treatment of Hodgkin's disease; Carry or have a first-degree relative who carries a genetic mutation in the TP53 or PTEN genes.

Several issues need to be considered when determining who should be screened and what method should be used. These include risk stratification, age to begin screening, how often to perform screening and at what age to stop screening. Most agree that routine screening mammography should be offered to women ages 50-69. The controversy lies in patients between the ages of 40 and 49 and those over 70. Many agree that for older patients who are in good health and would be able to undergo treatment, screening should be offered. Patients with significant comorbidities or those with a life expectancy of less than five years, (i.e., those patients in whom intervention is unlikely if breast cancer is found) probably should not be screened. The interval at which to perform screening is another issue with some controversy; typically, breast cancers grow more

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[57] Debbie Saslow et al., "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography," *CA: A Cancer Journal for Clinicians* 57, no. 2 (April 2007): 75–89.
[58] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

slowly in older women therefore, it may be reasonable to extend the interval in those patients over the age of 50. [59]

For those patients who are carriers of either BRCA1 or 2, the NCCN and the ACS recommend the following strategy for screening: [60]: Monthly breast self-exams beginning at age 18; Clinical breast exams 2 to 4 times annually beginning at age 25; Annual mammography and breast MRI beginning at age 25, or depending on the earliest age of onset in family.

The NCCN stratifies women into two basic risk categories for screening purposes, those at normal risk and those at increased risk. Increased risk includes five separate groups, women who have received thoracic or mantle irradiation, women ages 35 and older who have a five-year risk of invasive carcinoma of 1.7% or lifetime risk of > 20%, women with a strong family history or genetic predisposition, women with LCIS or atypical hyperplasia, and women with a prior history of breast cancer. Table 1.4 lists the screening recommendations for each risk group as designated by the NCCN. [61]

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[59] Ibid.; Saslow et al., "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography."

[60] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011"; Saslow et al., "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography."

[61] NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

Table 1.4 NCCN Breast Cancer Screening Recommendations by Risk [62]

Group	Screening Recommendation
Women at Normal Risk	
Ages 20-39	CBE Every 1-3 Years
Ages ≥40	Annual CBE with SM
Women at Increased Risk	
Thoracic Irradiation	For patients <25: annual CBE For patients ≥25: CBE every 6-12 months and annual SM beginning 8-10 years post-RT or age 25 whichever occurs last Possible annual breast MRI
≥35 with 5-Year Risk of ≥ 1.7% or LCIS	CBE every 6-12 months and annual SM Consider risk-reduction strategies
Lifetime Risk of >20%	CBE every 6-12 months and annual SM; consider risk-reduction strategies and annual breast MRI
Strong Family History or Genetic Predisposition	For patients <25, annual CBE and consider referral to genetic counselor, For patients ≥25, CBE every 6-12 months, annual SM beginning 5-10 years prior to the youngest breast cancer case in the family, and annual breast MRI, consider risk-reduction strategies and referral to genetic counselor

CBE: Clinical Breast Exam; SM: Screening Mammography; MRI: Magnetic Resonance Imaging; LCIS: Lobular Carcinoma *in situ;* RT: Radiotherapy

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[62] Ibid.

Screening for breast cancer can also have limitations/problems. Besides the actual physical discomfort experienced by women undergoing the screening and the radiation exposure, there is a risk of false positives and over-diagnosis. Over-diagnosis of breast cancer happens when screening leads to diagnosis of abnormalities such as ductal carcinoma *in situ* (DCIS), which would not be diagnosed without screening, and are unlikely to develop into invasive carcinomas. In a systematic review by Jorgenson and Gotzsche, the authors pooled incidence results from five trials describing population based screening efforts. They included only incidence figures from the final year of observation. Trials had over diagnosis estimates ranging from 44-57%. The pooled effect size was concluded to be 52% (95% CI: 46 -58%). [63]

Clinicians, however, are more concerned with false positive readings as women can be harmed as a result of a false positive finding. This subsequently leads to unnecessary testing and treatment, and subjecting patients to procedures whom are without the disease. Factors that may increase the number of false positives include: younger patients, increased number of breast biopsies, a positive family history of breast cancer, hormone replacement therapy, increased interval between screenings, and lack of prior results. The numbers of false positives are also higher in patients with increasing breast density. False positives are more common in younger women both because the test is less specific and breast cancer in that age group is less common. As a result, more biopsies are performed on younger women and fewer cancers are found. There are similar concerns in screening older women or women taking hormone therapy. Recommendations to reduce the number of false positives include: encouraging patients not to wait more than 18 months between screenings, obtain prior results for comparison

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[63] K. J. Jorgensen and P. C Gotzsche, "Overdiagnosis in Publicly Organised Mammography Screening Programmes: Systematic Review of Incidence Trends," *BMJ* 339, no. jul09 1 (July 9, 2009): b2587–b2587.

especially if switching providers, and to refer patients to experienced radiologists who do not have more than a 10% recall rate. [64]

The majority of breast cancers (approximately 90%) are diagnosed as a result of an abnormal mammogram. After an abnormal mammogram, further evaluation is conducted. Diagnostic evaluations can include one or more of the following: diagnostic mammography, ultrasonography, breast MRI and tissue sampling. Usually, a diagnostic mammogram with or without ultrasonography is performed to determine if there is a need for tissue sampling. The diagnostic mammography is different from screening mammography in that the latter uses two standard x-ray views, and the diagnostic mammography uses additional views to evaluate a positive finding. [65]

Breast ultrasonography is a complement to mammography, and can be used to differentiate between cystic and solid masses that are palpable or detected on mammograms. It can be used for guidance in interventional procedures. When a mass detected on physical exam is poorly visualized on mammogram, breast ultrasonography is useful. Poor visualization can occur as a result of highly dense breast tissue; therefore, ultrasonography may provide utility. Ultrasonography can also be used in patients who have a detected mass on a mammogram that is consistent with fibroadenoma or a benign cyst. It can also be used to determine whether a suspicious lesion on mammogram can be evaluated with a biopsy and to determine whether neoadjuvant therapy is appropriate in patients presenting with large or locally advanced tumors.

Ultrasonography is recommended for women <30 who present with a lump or mass or asymmetric thickening or nodularity and in women >30 who present with a lump

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[64] L. L Humphrey et al., "Breast Cancer Screening: a Summary of the Evidence for the US Preventive Services Task Force," *Annals of Internal Medicine* 137, no. 5 Part 1 (September 3, 2002): 347–360.

[65] Laura J. Esserman and Bonnie N. Joe, "Diagnostic Evaluation of Women Suspected With Breast Cancer," *Up To Date*, September 2009, www.uptodate.com.

or mass and a mammography finding of BI-RADS 1-3. Ultrasonography may also be a consideration in patients of any age if skin changes are suggestive of serious breast disease and in women with BI-RADS Category 0. Table 1.5 lists each BI-RADS category, the corresponding finding, and the likelihood ratio of that finding leading to a diagnosis of breast cancer. [66]

A biopsy is recommended if the results of a diagnostic mammogram or ultrasonography are indeterminate or suspicious. Micro-calcification and soft tissue density are the primary findings that are indications for biopsy after a mammogram. Biopsy could include a fine needle aspirate (FNA), core needle biopsy (CNB), excisional biopsy with or without wire or tack localization, or duct excision with or without ductography. [67]

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[66] W. A Berg et al., "Combined Screening with Ultrasound and Mammography Vs Mammography Alone in Women at Elevated Risk of Breast Cancer," *Jama* 299, no. 18 (2008): 2151; K. Flobbe et al., "The Additional Diagnostic Value of Ultrasonography in the Diagnosis of Breast Cancer," *Archives of Internal Medicine* 163, no. 10 (2003): 1194; NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

[67] Esserman and Joe, "Diagnostic Evaluation of Women Suspected With Breast Cancer"; NCCN Breast Cancer Panel Members, "Breast Cancer Screening and Diagnosis V1.2011."

Table 1.5 ACR BI-RADS Categories[68]

Category	Finding	LR
0	Incomplete Assessment	7
1	Negative	0.1
2	Benign	0.1
3	Probably Benign - Short Interval Follow-up Suggested	1.2
4	Suspicious Abnormality-Biopsy Should be Considered	125
5	Highly Suggestive of Malignancy - Immediate Action Should be Taken	2200
6	Known Biopsy - Proven Malignancy	

BC: Breast Cancer; LR: Likelihood Ratio

1.3.5 STAGING/CLASSIFICATION

Staging is useful for clinicians because it assists in choosing treatment modalities and helps predict prognosis. Staging of breast cancer is typically done with the same staging system as other cancers, which is the TNM system which uses characteristics from the tumor, lymph nodes involved and metastasis to determine stage. The stage of disease is determined by using the TNM classification system. Each designation for tumor size, lymph node involvement and existence of metastases correspond to a disease stage. Stage designations and corresponding TNM values are listed in Table 1.6. [69]

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[68] American College of Radiology, "BI-RADS® – Mammography, Fourth Edition," Professional Organization, *American College of Radiology*, 2003, http://www.acr.org/; Elmore et al., "Screening for Breast Cancer."

[69] S. E. Singletary and J. L. Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual," *CA: A Cancer Journal for Clinicians* 56, no. 1 (January 2006): 37–47; ibid.

Table 1.6 Stage Designation Based on TNM Classifications[70]

Stage Designation	Tumor Size	Node Involvement	Metastases
0	T_{is}	N0	M0
I	T1	N0	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

TNM: Tumor, Node, Metastasis

However, to accommodate changes with regard to classification, screening and diagnosis such as the use of screening mammography, use of sentinel lymph node biopsy, and changes in the approach to distant metastases that are common in breast cancer, supplementary detail were added. Additional caveats to the previous system account for detection of earlier disease and much smaller tumors and it has been adapted to reflect the change in standard of care from axillary lymph node dissection to the use of sentinel lymph node dissection. [71] Another reason that called for a change in the classic TNM classification was that therapy options are often determined by stage designation or TNM classifications. In the previous system, ductal carcinoma *in situ* (DCIS) or lobular

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[70] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual."

[71] Ibid.

carcinoma *in situ* (LCIS) were grouped with malignant disease. The current thinking is that since *in situ* disease lacks the ability to metastasize, it should not be categorized as malignant. [72]

The TNM staging system includes four classifications: clinical, pathologic, recurrence, and autopsy, designated as cTNM, pTNM, rTNM and aTNM respectively. Clinical is used for local/regional treatment choices, pathologic is for prognosis or adjuvant treatment choices, recurrence is used when further treatment is necessary after disease recurrence, and autopsy is for cancers discovered post-mortem. [73]

In the TNM classification system, T refers to the tumor size. Tumor size must be measured before any tissue is removed, and it is a measurement of the invasive component only. The largest primary carcinoma is used to designate the T classification. The most recent revision to the classification system gave sub-categories to the T1 stage because evidence suggested differing outcomes and treatment needs on what was formerly just considered "micro-metastasis". Table 1.7 lists each tumor classification and the corresponding definition. [74]

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[72] Ibid.; ibid.; Umberto Veronesi et al., "Rethinking TNM: Breast Cancer TNM Classification for Treatment Decision-making and Research," *The Breast* 15, no. 1 (2006): 3–8.

[73] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual"; Wendy A. Woodward et al., "Changes in the 2003 American Joint Committee on Cancer Staging for Breast Cancer Dramatically Affect Stage-Specific Survival," *Journal of Clinical Oncology* 21, no. 17 (2003): 3244–3248.

[74] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual"; S. Eva Singletary et al., "Revision of the American Joint Committee on Cancer Staging System for Breast Cancer," *Journal of Clinical Oncology* 20, no. 17 (September 2002): 3628–3636.

Table 1.7 Breast Cancer Tumor (T) Classifications[75]

Classification		Criteria
Tx		Primary tumor cannot be assessed
T0		No evidence of tumor
Tis		Carcinoma *in situ*
T1		≤ 2 cm
	T1mic	≤ 0.1 cm
	T1a	> 0.1 - 0.5 cm
	T1b	> 0.5 – 1 cm
	T1c	> 1 – 2 cm
T2		> 2 – 5 cm
T3		> 5 cm
T4		Any size; with direct extension to chest wall or skin
	T4a	Direct extension to chest wall (not including pectoralis muscle)
	T4b	Edema (including peau d'orange) or ulceration of skin or satellite skin nodules
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma

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[75] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual."

N refers to the clinical involvement of lymph nodes and pN refers to the pathologic involvement of lymph nodes. The difference lies in the method used to confirm the involvement of lymph nodes. Clinically apparent is confirmation that is detected via imaging studies or by clinical examination or those that are grossly visible pathologically, whereas, a classification of pN would be detected only using immunohistochemical (IHC) or molecular methods. If distant nodal involvement is determined solely by sentinel lymph node biopsy (SLNB), a designation of (sn) will follow the classification. Isolated tumor cells (ITCs) are designated with (i+). Tables 1.8 and 1.9 list the clinical and pathologic classifications for lymph nodes and their corresponding definitions. [76]

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[76] Ibid.; Singletary et al., "Revision of the American Joint Committee on Cancer Staging System for Breast Cancer."

Table 1.8 Clinical Lymph Nodes (N) Classification for Breast Cancer [77]

Classification		Criteria
Nx		Regional lymph nodes cannot be assessed (e.g. previously removed)
N0		No regional Lymph node metastasis
N1		Metastasis in movable ipsilateral axillary lymph node(s)
N2		Metastasis in axillary lymph(s) fixed or matted, or in clinically apparent ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis
	N2a	Metastasis in axillary lymph node(s) fixed to one another (matted) or to other structures
	N2b	Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3		Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent ipsilateral internal mammary node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary node involvement
	N3a	Metastasis in ipsilateral infraclavicular node(s) and axillary lymph node(s)
	N3b	Metastasis in ipsilateral internal mammary node(s) and axillary lymph node(s)
	N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

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[77] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual."

Table 1.9 Pathologic Lymph Nodes (pN) Classification for Breast Cancer [78]

Classification	Criteria
pN0	No regional lymph node metastasis histologically
pN1mi	Micrometastasis (> 0.2 mm, none > 2mm)
pN1	Metastasis in 1 - 3 axillary lymph nodes and/or internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN2	Metastasis in 4 - 9 axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in $\geq$ 10 axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes or in ipsilateral supraclavicular lymph nodes

mm: millimeter

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[78] Ibid.

M refers to whether the patient presents with distant metastases and is essentially scored as either yes, no or cannot be assessed. In cases where distant metastases cannot be assessed, a designation of MX is given, although a negative history and physical exam are usually enough to give a designation of M0. Table 1.10 lists each classification and corresponding criteria for metastases [79]

Table 1.10 Classification of Distant Metastasis (M) for Breast Cancer [80]

Classification	Criteria
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant Metastasis

1.3.6   TREATMENT OPTIONS

Treatment strategies are determined based on the stage of disease in which the patient has presented.   Treatments are defined as either local or systemic. Local treatments include surgery and radiation, while drug therapies are considered systemic. Drug therapies may be given as neoadjuvant (before surgery or radiation to shrink tumor size) or as adjuvant therapy (after surgery or radiation to prevent recurrence). Modalities

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[79] Ibid.; Singletary et al., "Revision of the American Joint Committee on Cancer Staging System for Breast Cancer."

[80] Singletary and Connolly, "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual."

include surgical options ranging from breast conserving surgery to total mastectomy with or without breast reconstruction, radiation, and drug therapy, which can include cytotoxic agents, hormone agents, and targeted agents. [81]

1.3.6.1   Surgery

Surgery is usually part of every patient's treatment. Decades ago the standard of care in surgical treatment was total mastectomy of the affected breast. Now, eligible early stage patients may choose to have a lumpectomy or breast conserving surgery. Lumpectomy is when the tumor itself is removed, typically along with the lymph nodes in the armpit of the affected breast. Lymph node removal is meant as an additional diagnostic tool. If the tumor is invasive and clear margins are not obtained, additional therapies are required (i.e., radiation). For women with stage I or II cancer, lumpectomy plus radiation is an effective strategy. Evidence suggests that lumpectomy plus radiation is as successful as total mastectomy in patients with theses stages of disease. [82]

Breast conserving surgery (BCS), which is also known as a quadrantectomy, is a procedure that removes the tumor and surrounding breast tissue, and sometimes includes the lining over the chest muscle. BCS is more invasive than a lumpectomy but much less invasive than a total mastectomy. Quadrantectomy plus radiotherapy provides similar results to total mastectomy in women with early stage disease. BCS is predicated on achieving a pathologically negative margin of resection. Those patients that have a positive margin will need to undergo more surgery, which may include additional

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[81] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011," Professional Organization, *National Comprehensive Cancer Network*, March 25, 2011, www.nccn.org.
[82] Ibid.

excision or mastectomy. If multiple margins are positive, mastectomy will generally be required. [83]

A total mastectomy involves removing the entire breast and often lymph nodes from the armpit, whereas a radical mastectomy involves removing the breast, the chest muscles, all of the lymph nodes from under the arm and some additional fat and skin. A modified radical mastectomy removes the entire breast, armpit lymph nodes and underlying chest wall muscle. There are usually no survival benefits to performing a radical mastectomy compared to the less invasive methods. [84]

After a mastectomy, women can elect to have breast reconstruction or prosthesis, and this can be done at the same time the tissue is removed. Saline or silicone implants have been used and do not affect the rate of breast cancer recurrence. Patients can also elect to have reconstruction, which uses muscle tissue from elsewhere in their own body. Typically, if radiation is required post-surgically, reconstruction will have to be done after radiation. Some studies show that women who elect to have reconstruction surgery report better overall well-being and health-related quality-of-life (HRQoL). [85]

1.3.6.2   Radiation

In initial treatment, radiation can be administered either before or after surgery. High powered x-rays are used to kill or shrink cancer cells. Radiation can be used for weeks following surgery to reduce cancer recurrence in the breast and chest wall. Radiation can also help alleviate symptoms and slow progression and is appropriate for use in patients of all ages, including those over 65. Radiation therapy is administered

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[83] Ibid.

[84] Ibid.

[85] Ibid.

usually four to six weeks after surgery as external beam radiation, where x-rays are delivered directly to either the whole breast or the lumpectomy surgical bed and chest wall in high risk patients (which includes those with close surgical margins, large tumors or lymph node involvement). Treatment is daily (5 days per week) for three to six weeks; shorter courses are occasionally used for patients with early stage disease. Radiation can also be administered as an implant (brachytherapy) and can be used after whole breast irradiation. [86]

Partial breast irradiation (PBI) is now considered an option because recurrence is often found near the original lumpectomy surgical bed. The NCCN recommends that PBI only be used in patients with a low risk of recurrence. Careful selection of patients is important to the success of PBI; appropriate patients would include those older than 45 with unifocal, invasive ductal carcinoma that measures less than three cm with negative microscopic surgical margins and negative lymph nodes. Interstitial brachytherapy and inflatable balloon interstitial catheters are types of partial breast irradiation, however since brachytherapy requires an enormous amount of technical expertise, it is now done less frequently with the introduction of the balloon catheter method, which is now used extensively worldwide. PBI or brachytherapy is often used as a "boost" to the tumor bed in patients with an elevated risk of failure. These include patients younger than 50, positive axillary lymph nodes, lymphovascular invasion or close margins. [87]

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[86] Ibid.
[87] Ibid.

1.3.6.3　Chemotherapy

Chemotherapy is a part of all treatment regimens for advanced disease and can be used in early disease as well. A general principle of cancer therapy is to tailor the chemotherapy choice to the type of cancer. Choice of chemotherapy can depend on whether the tumor is node-positive or node-negative, hormone receptor positive or negative or HER-2 positive or negative. In addition, different approaches are used depending on whether the patient presents with early or advanced disease. Neoadjuvant chemotherapy is administered before surgery or radiation, and adjuvant is started after surgery but usually before radiation. Delaying chemotherapy for more than twelve weeks post-surgery increases the rate of recurrence and may increase mortality. Tables 1.11 and 1.12 give the recommended chemotherapy regimens for the treatment of breast cancer. [88]

Classes of agents used in breast cancer are anthracyclines including doxorubicin (Adriamycin®) and epirubicin (Ellence®), which are used in regimens for both early and advanced disease. Taxanes, including paclitaxel (Taxol® and Abraxane®) and docetaxel (Taxotere®), appear to be particularly useful in node-positive disease, and Abraxane® is used as secondary treatment for advanced disease. Platinum agents including oxaliplatin (Eloxatin®) and carboplatin (Paraplatin®) are used in combination regimens for advanced disease and for cancers associated with BRCA genes. Treatment regimens usually consist of four to six cycles that are given over three to six months. [89]

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[88] Ibid.
[89] Ibid.

Table 1.11 Common Adjuvant Chemotherapy Regimens Used in Breast Cancer[90]

Regimen Type	Drugs and Sequencing
Adjuvant-Preferred	AC
	AC→ Paclitaxel
	Dose Dense AC → Paclitaxel
	TC
	TAC
Adjuvant-Other	FAC
	FEC
	CAF
	Paclitaxel → FAC
	AC → Docetaxel
	AC → Paclitaxel
	EC
	A→ Paclitaxel → C
	CMF
	FEC→T
Trastuzumab-Preferred	AC→ Paclitaxel + H
	TCH
Trastuzumab-Other	T+H→FEC
	AC→ Docetaxel + H
Trastuzumab-Neoadjuvant	Paclitaxel + H → CEF + H

See Appendix A for Regimen Abbreviations and Appendix B for Regimen Schedules

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[90] Ibid.

Table 1.12 Common Metastatic Chemotherapy Regimens Used in Breast Cancer[91]

Regimen Type	Drugs/Sequencing
Single Agent-Preferred	Paclitaxel/Albumin-Bound Paclitaxel Vinorelbine Docetaxel Gemcitabine Capcitabine Doxorubicin or Liposomal Doxorubicin Epirubicin
Single Agent-Other	Cyclophosphamide Mitoxantrone Cisplatin Etotoposide (Oral) Vinblastine Fluorouracil Ixabepilone
Combinations-Preferred	Docetaxel + Capcitabine Paclitaxel + gemcitabine CAF FEC AC EC AT CMF Bevacizumab + Paclitaxel
Combination- Other HER-2 (+) first Line	Ixabepilone + Capcitabine Paclitaxel ± Carboplatin Docetaxel Vinorelbine Capcitabine
Preferred for HER-2 (+) Trastuzumab Exposed	Lapatinib + Capcitabine H + Other First-Line H + Capcitabine H + Lapatinib

See Appendix A for Regimen Abbreviations and Appendix B for Regimen Schedules

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[91] Ibid.

1.3.6.4   Hormone Therapy

NCCN guidelines state that estrogen receptor (ER) and progesterone receptor (PR) status should be determined in all primary invasive breast cancers. All patients who are ER or PR receptor positive should be offered adjuvant hormone therapy regardless of age, node status, or whether adjuvant chemotherapy is planned. There is evidence that some HER-2 positive tumors may be less sensitive to endocrine therapy, although these findings have yet to be confirmed. The ATAC trial concluded that HER-2 positive status did render some patients resistant to endocrine therapies; however, since the side effect profile of endocrine agents is favorable, the recommendation remains to give endocrine therapy to patients whose tumors test ER or PR positive regardless of HER-2 status, pre- or post-menopause, or age. The exception is those patients with small tumors where there is little expected benefit with the addition of hormone therapy. Pre-menopausal patients should have ovarian ablation or suppression followed by recommendations for postmenopausal patients, which include the use of: non-steroidal aromatase inhibitor (anastrazole or letrozole), steroidal aromatase inactivator (exemestane), fulvestrant, tamoxifen or toremifene, megesterol acetate, fluoxymesterone, or ethinyl estradiol. Endocrine therapies are to be given sequentially, not concurrently, with chemotherapy. [92]

1.3.6.5   Trastuzumab

Trastuzumab is a monoclonal antibody with activity against the HER-2 receptor protein. The drug acts by binding a specific epitope of the HER-2 protein on the breast cancer cell surface. Once bound, the drug inhibits signal transduction that in turn inhibits cell growth. There are other proposed benefits such as reversal of resistance to endocrine

[92] Ibid.

therapies and augmentation of both cellular and humoral immunity. All patients diagnosed with breast cancer undergo HER-2 testing to select those who might benefit from the addition of trastuzumab to other regimens. Patients with metastatic disease who have a high level of HER-2 over-expression are likely to be sensitive to trastuzumab and see increased survival. There is also accumulating evidence that patients with earlier stage HER-2 positive disease can also benefit from the addition of trastuzumab in the adjuvant setting, giving up to a 50% reduction in recurrence. Current recommendations are that if patients test a 3+ IHC staining or amplified HER-2 genome copy number by FISH, they receive trastuzumab in the adjuvant or metastatic setting. [93]

1.3.7 RESPONSE TO THERAPY

Tumor response after administration of anti-cancer agents is evaluated for at least three purposes and those include: tumor response as a prospective end-point in an early clinical trial, as an end-point in a more definitive clinical trial, and as a guide for the clinician/study subject regarding the continuation of treatment. [94] There are criteria used to quantify how a patient responds to treatment, including the response evaluation criteria in solid tumors (RECIST) [95] and the South West Oncology Group (SWOG) response criteria, endpoint definitions and toxicity criteria. [96]

The RECIST guidelines are a voluntary international standard used to assess the response to treatment of measurable disease and are a simplification of other response

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[93] Ibid.

[94] E. A. Eisenhauer et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)," *European Journal of Cancer* 45, no. 2 (2009): 228–247.

[95] Ibid.; P. Therasse et al., "New Guidelines to Evaluate the Response to Treatment in Solid Tumors," *Breast Cancer* 12 (2005): 16–27.

[96] S. Green and G. R Weiss, "Southwest Oncology Group Standard Response Criteria, Endpoint Definitions and Toxicity Criteria," *Investigational New Drugs* 10, no. 4 (1992): 239–253.

criteria (i.e., ECOG and WHO). Table 1.13 lists the response criteria in the RECIST guideline. [97] There are plans to improve the RECIST guidelines to incorporate dynamic, functional contrast and volumetric imaging. There are hopes that the use of these more advanced imaging methods can be used as surrogate end points in clinical trials with the expectation that in future trial settings fewer patients would be required and this would improve efficiency in getting newer agents approved. [98]

Table 1.13 RECIST Response Criteria[99]

Response		Criteria
Complete Response	(CR)	Disappearance of all target lesions
Partial Response	(PR)	30% decrease in the sum of the longest diameter of target lesions
Progressive Disease	(PD)	20% increase in the sum of the longest diameter of target lesions
Stable Disease	(SD)	Small changes that do not meet any of the above criteria

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[97] Therasse et al., "New Guidelines to Evaluate the Response to Treatment in Solid Tumors."

[98] Eisenhauer et al., "New Response Evaluation Criteria in Solid Tumours."

[99] Therasse et al., "New Guidelines to Evaluate the Response to Treatment in Solid Tumors."

The SWOG criteria are more applicable to patients in the trial setting and differentiate between disease status and objective status. [100] Disease status can fall into one of three categories, measurable disease, evaluable disease, and non-evaluable disease. Measurable disease is defined as lesions with clearly defined margins that can be measured either with a plain photograph or x-ray to be ≥ 0.5 cm, palpation with diameters greater than 2 cm, CT, MRI or other imaging that shows a diameter greater than the cuts of the scan. Evaluable disease is defined as lesions with more poorly defined margins, lesions with diameters < 0.5 cm, lesions on imaging that have diameters less than the cuts of the scan, palpable masses with diameters < 2 cm or bone disease. Non-evaluable disease is that which is documented with indirect evidence only (i.e. lab values) such as pleural effusions or ascites. If the patient has too many lesions to measure, then three are followed and the rest are considered in the objective status.[101]

The objective status considers all lesions, not only the largest lesions, which are used to determine the disease status. A complete response (CR) is obtained when all evidence of measurable and evaluable lesions disappears, the patient is absent of any disease related symptoms and there is no evidence of non-evaluable disease. All measurements must be repeated with the same method used to obtain initial assessment of disease status. Partial response (PR) is a ≥ 50% decrease in sum total of all baseline criteria (i.e., diameter of all measurable lesions) without progression and no new lesions. A partial response in non-measurable disease (PRNM) is disease specific. Progression (P) is when there is a 50% increase or an increase of 10 cm whichever is smaller in the sum total of all lesion diameters or a clear progression in evaluable disease, or reappearance of

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[100] Green and Weiss, "Southwest Oncology Group Standard Response Criteria, Endpoint Definitions and Toxicity Criteria."
[101] Ibid.

a lesion that has disappeared, or appearance of new lesion, or death. The patient may have unknown response because it could not be evaluated. Stable or No response is disease that does not qualify for CR, PR or P. [102]

Performance status can be used as a surrogate to other, more objective, findings to indicate a patient's disease progression and potential prognosis. These measures could also be considered a proxy to determine if patients are tolerating treatment and if the level of their disease is affecting their ability to perform activities of daily living. [103] Examples of scales used to measure a patient's performance status include the Eastern Cooperative Oncology Group (ECOG) Performance Status, which is also known as the WHO or Zubrod scale, and the Karnofsky Performance Status (KPS). [104]

The Eastern Cooperative Oncology Group (ECOG) has a scale (Table 1.14) that was developed in 1982 and is still commonly used by physicians and researchers to assess how a patients' disease is progressing, assess how the disease is affecting activities of daily living and determine appropriate treatment and prognosis. The scale focuses on activity the patient is capable of doing; therefore, if the patient is hospitalized for an unrelated reason and can still carry on pre-disease performance, then that patient would be given a grade of zero. [105]

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[102] Ibid.

[103] M Ando et al., "Prognostic Value of Performance Status Assessed by Patients Themselves, Nurses, and Oncologists in Advanced Non-small Cell Lung Cancer," *British Journal of Cancer* 85, no. 11 (November 2001): 1634–1639.

[104] Amy P. Abernethy et al., "The Australia-modified Karnofsky Performance Status (AKPS) Scale: a Revised Scale for Contemporary Palliative Care Clinical Practice," *BMC Palliat Care* 4, no. 7 (2005): 4–7; Martin M. M.D. Oken et al., "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group," *Journal of Clinical Oncology December 1982* 5, no. 6 (1982): 649–656; Therasse et al., "New Guidelines to Evaluate the Response to Treatment in Solid Tumors"; Charles G. Zubrod et al., "Appraisal of Methods for the Study of Chemotherapy of Cancer in Man: Comparative Therapeutic Trial of Nitrogen Mustard and Triethylene Thiophosphoramide," *Journal of Chronic Diseases* 11, no. 1 (January 1960): 7–33.

[105] Oken et al., "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group"; Therasse et al., "New Guidelines to Evaluate the Response to Treatment in Solid Tumors."

Table 1.14 ECOG Grades and Criteria for Performance Statuses[106]

Grade	ECOG Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG: Eastern Cooperative Oncology Group

The Karnofsky Performance Status (KPS) instrument was developed in the 1940's and is commonly used as a proxy measure for a cancer patient's quality of life, although the scale does not meet contemporary criteria to be considered a QOL measure. It allows patients to be classified according to their functional impairment and can give a sense of prognosis and appropriateness for treatment. The scale ranges from zero to 100, where 100 represents perfect health and zero represents death. It can be used as a subjective measure of a therapy's effectiveness and prognosis where lower scores indicate a poorer

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[106] Oken et al., "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group."

outcome. (Table 1.15)[107] The KPS is similar to the Global Assessment of Functioning (GAF) in the DSM-IV. [108] There are also several modified indices that are used to make the scale more relevant to today's practice. The Thorne-Modified KPS focuses on community based care and is more relevant to palliative care practices. The Australian Modified KPS is a hybrid of original KPS and the Thorne-Modified KPS. [109]

[107] Abernethy et al., "The Australia-modified Karnofsky Performance Status (AKPS) Scale."

[108] I. H. Monrad Aas, "Guidelines for Rating Global Assessment of Functioning (GAF)," *Annals of General Psychiatry* 10, no. 2 (2011), http://www.ncbi.nlm.nih.gov/pubmed/21251305.

[109] Abernethy et al., "The Australia-modified Karnofsky Performance Status (AKPS) Scale."

Table 1.15 Karnofsky Performance Status Scale (KPS) Definitions and Rating (%) Criteria[110]

Definition	Score	Original KPS Criteria
	100	Normal no complaints; no evidence of disease.
Able to carry on normal activity and to work; no special care needed	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Death

KPS: Karnofsky Performance Index

1.3.8 SURVEILLANCE/FOLLOW-UP

The NCCN has guidelines for follow-up for those patients treated in Stages 0-3 and for initial workup for stage four. [111] This includes an interval history and physical exam every four to six months for the first five years, then annually. During that office visit, the patient will likely have lab work performed including: complete blood count (CBC), platelets, and liver function tests (LFT's). They can expect periodic radiologic

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[110] Ibid.

[111] NCCN Breast Cancer Panel Members, "NCCN."

procedures as well, which typically include chest x-rays, bone scans, and x-rays of any bones experiencing symptoms or long weight-bearing bones appearing abnormal on bone scan. Abdominal CT or PET scan can be performed although it is generally not encouraged unless other studies have suspicious or equivocal results. Patients will be advised to get a mammogram every 12 months starting 6 - 12 months after radiation for those patients who elected to have breast conserving surgery. Women who are taking tamoxifen are advised to have a gynecological exam annually if they have an intact uterus, and women who are taking aromatase inhibitors or those who experience ovarian failure due to treatment need to have a bone density scan at baseline and be monitored periodically. [112]

ASCO also has a guideline for surveillance. They recommend that patients return for an exam every 3 to 6 months for three years, every 6 - 12 months for two years, then annually thereafter. In addition, ASCO recommends monthly self-exams and annual mammograms; however, they do not recommend laboratory or radiological tests during routine surveillance. [113] Additionally, if patients present with recurrent disease, they may have additional biopsies and HER-2 and ER/PR receptor status testing if status was originally unknown or negative. [114]

A recent Cochrane review concluded that surveillance of patients (in stage I, II or III disease) using intensive measures (i.e. laboratory tests and radiological procedures)

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[112] Ibid.

[113] Harold J. Burstein and Eric P. Winer, "Primary Care for Survivors of Breast Cancer," *New* 343, no. 15 (October 12, 2000): 1086–1094.

[114] Arti Hurria and Clifford Hudis, "Follow-up Care of Breast Cancer Survivors," *Critical Reviews in Oncology/Hematology* 48, no. 1 (2003): 89–99; J. L. Khatcheressian et al., "American Society of Clinical Oncology 2006 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting," *Journal of Clinical Oncology* 24, no. 31 (November 2006): 5091–5097.

did not yield significant improvements in mortality and thus, cannot be recommended. [115] Contrary to that review, it is still common to tailor follow-up much in the same way initial therapy is individualized. [116]

1.3.9   DISEASE RECURRENCE

Recurrence is most often seen within five years but may present as late as ten years after initial diagnosis. [117] The risk of recurrence is proportional to the grade and stage of tumor at initial diagnosis and is reduced by appropriate therapy. Further evaluation is indicated in patients presenting with non-specific symptoms including reports of new bone pain, shortness of breath, or neurological symptoms or if patient presents with jaundice. [118] Symptoms suggestive of recurrence include: change in chest wall, adenopathy, weight loss, persistent cough, cardiopulmonary symptoms and musculoskeletal pain. [119] Additional blood, radiological procedures or tumor-marker testing is not recommended in patients who are asymptomatic, in fact, this often leads to false-positives, which increase anxiety and stress along with overall treatment costs. [120]

If there is a recurrence of disease, the patient receives the same treatment as a patient diagnosed with stage 4 breast cancer, where therapy choices depend on whether there is local or systemic disease. Local disease in recurrence is treated much the same as

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[115] M.P. Rojas et al., "Follow-Up Strategies for Women Treated for Early Breast Cancer," *The Cochrane Database of Systematic Reviews*, no. 4 (2009), http://www2.cochrane.org/.

[116] Eva Grunfeld, "Optimizing Follow-up After Breast Cancer Treatment," *Current Opinion in Obstetrics and Gynecology* 21, no. 1 (2009): 92–96.

[117] Burstein and Winer, "Primary Care for Survivors of Breast Cancer."

[118] Daniel F. Hayes, "Follow-up of Patients with Early Breast Cancer," *N Engl J Med* 356, no. 24 (June 14, 2007): 2505–2513.

[119] Burstein and Winer, "Primary Care for Survivors of Breast Cancer."

[120] Hayes, "Follow-up of Patients with Early Breast Cancer."

earlier stage disease, where initially the patient will receive some type of surgical intervention to reduce tumor burden. This choice depends on the initial surgery performed, where patients who elected for lumpectomy or breast conserving surgery will undergo a mastectomy and will have axillary node dissection if it was not previously done. Patients who already had a mastectomy, resection of the tumor will be performed if possible. Additionally, patients who did not have prior radiation will undergo radiation on recurrence. All patients will be considered for additional systemic therapies. The choice of therapy will depend on what the patient initially received, in addition to their hormone receptor and HER-2 status. [121]

Patients who are hormone receptor positive will receive some type of endocrine therapy with or without ovarian ablation. This therapy will continue until progression or there is unacceptable toxicity. Chemotherapy is considered if the patient has had three consecutive failed courses of endocrine therapy or presents with symptomatic visceral disease. If hormone receptor positive patients are also HER-2 positive, they will likely receive trastuzumab. Patients who are hormone receptor negative or refractory may receive a trial of endocrine therapy with chemotherapy. Chemotherapy is continued until there is no response to three sequential regimens or the patient's ECOG performance status is ≥ 3 at which point the patient is transitioned to palliative care. [122]

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[121] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."
[122] Ibid.

1.3.10 NON-CARDIAC CONSEQUENCES OF THERAPY

Surveillance of patients at the conclusion of treatment serves a number of purposes. Those include the detection of recurrent disease, the detection of a second primary tumor, and management of short and long term side effects. [123] Breast cancer treatment, similar to the treatment of any disease, is not without consequences. Consequences of therapy can be divided into local and systemic effects, both with unique risk factors. The adverse effects that are experienced by patients can range in severity, which is commonly related to the quantity of the offending therapy the patient received. Detection of effects can be monitored in a number of ways which can include physical exams, laboratory tests, and radiological procedures. [124]

Treatment recommendations for breast cancer include the use of both local (surgery/radiation) and systemic (cytotoxic and/or hormonal) therapies. [125] Local therapies include surgery and radiation, both of which are mainstays of breast cancer treatment. Effects from surgical intervention have been reported in patients up to 20 years after the procedure. The primary negative effect reported is lymphedema, which occurs as a result of lymph node removal. Risk of lymphedema is related to the extent of the lymph node dissection that is performed (i.e., risk is higher if all nodes are removed). The extent of node removal is typically dependent on whether metastatic disease is detected in the sentinel lymph node examination. [126] Other consequences related to surgery include seroma formation (can be prevented by leaving drains in place), pain, numbness,

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[123] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

[124] Ibid.

[125] Ibid.; NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

[126] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

limitations in range of motion, and weakness. These are often related to the type of surgery performed. [127]

Consequences of radiation treatment that was performed with outdated techniques, involved an increase in death from cardiac causes, however, this has decreased significantly with newer techniques. There is no shown increase in cardiac toxicity in women who receive standard doses of anthracyclines; however, this risk increases as cumulative anthracycline dose also increases. [128]

Immediate effects of radiation therapy include nausea, vomiting, and fatigue, all of which typically get worse as treatment progresses. Short term side effects of radiation include pigmentation changes, skin burns, decreased range of motion and swelling of the arm on the affected side, and mild myelosuppression. The long term effect from radiation is the increased risk of other malignancies (more common in younger patients), rare occurrences of lung scarring. Malignancies after radiation therapy can include contralateral breast cancer, sarcoma, leukemia and myelodysplasias, ipsilateral lung cancer, and esophageal cancer.[129] Other effects include: pneumonitis, rib fracture, brachial plexopathy, and myocardial infarction. Additionally, women who receive radiation to the axilla after axillary dissection are at increased risk of lymphedema. All of these effects are decreased in patients receiving PBI as opposed to WBI. [130]

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[127] Ibid.
[128] Ibid.
[129] Ibid.
[130] Ibid.

Table 1.16 Common Complications of Local Breast Cancer Treatment and Corresponding Risk Factors [131]

Complication	Risk Factor
Common (Affecting > 10% of Patients)	
Pain or numbness in breast, chest wall, or axilla	Greater extent of surgery
Arm swelling or lymphedema	Greater extent of axillary surgery, weight gain, obesity, radiation therapy or infection
Restriction of arm motion or weakness	Greater extent of surgery, radiation therapy, recent surgery
Re-operation after breast-implantation reconstruction	Radiation therapy
Uncommon (Affecting 1 - 10% of Patients)	
Cellulitis	Radiation, seroma
Plexopathy or Nerve Damage	Higher dose of radiation or larger field
Contralateral Breast Disease	Familial or hereditary breast cancer, younger age at diagnosis, higher dose of radiation or larger field
Increased Risk of Heart Disease	Left-sided radiation with older techniques, anthracycline-based chemotherapy
Pneumonitis	Larger radiation field, older age, chemotherapy
Rib Fracture	Higher dose of radiation or larger field
Rare (affecting < 1% of patients)	
Secondary Cancers (other than breast)	Lymphedema, radiation therapy
Arterial Insufficiency	Radiation therapy
Pulmonary Fibrosis	Radiation therapy

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[131] Burstein and Winer, "Primary Care for Survivors of Breast Cancer."

Systemic therapies used include chemotherapy, endocrine therapy, and targeted agents; each therapy has its own unique adverse effect profile.[132] The use of systemic agents in breast cancer is individualized where treatment regimens are selected based on a patients stage at diagnosis, node status, HER-2 status and estrogen/progesterone receptor status, therefore, a wide range of effects could be experienced by each patient. [133] Chemotherapy has a number of consequences, some subside at the conclusion of treatment while others can appear months to years after treatment has concluded. Common side effects of virtually all chemotherapy agents include gastrointestinal issues (such as nausea, vomiting and stomatitis), reduced white blood cell and platelet counts, infections, and alopecia. [134]

Premature ovarian failure is a risk with a number of different chemotherapy agents; the risk varies with the regimen received, cumulative dose and the age of the patient. Ovarian failure is common in patients over 40 years of age with the incidence ranging from 80 to 95% but rarely occurs in women under the age of 30 with an estimated incidence of 19%. Ovarian failure and subsequent premature menopause is a result of decreased circulating estrogen and progesterone levels and increased follicle stimulating hormone and luteinizing hormones, these changes are consistent to those seen in naturally occurring menopause. [135] Although, pregnancy post-therapy has not been shown to affect breast cancer prognosis, it is common for clinicians to recommend that patients wait two to three years after the conclusion of therapy as this is the time disease recurrence is highest. [136]

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[132] Charles L. Shapiro and Abram Recht, "Side Effects of Adjuvant Treatment of Breast Cancer," *N Engl J Med* 344, no. 26 (June 28, 2001): 1997–2008.

[133] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

[134] Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

[135] Burstein and Winer, "Primary Care for Survivors of Breast Cancer."

[136] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

Survivors of breast cancer theoretically are at a lower risk of developing osteoporosis because of the role estrogen plays in disease development, it also acts to increase bone density, however, patients experiencing premature ovarian failure experience bone loss similar to menopausal women.[137] Hot flashes, coupled with osteoporosis, are experienced secondary to premature ovarian failure. Not unlike hot flashes experienced by women without breast cancer, these can profoundly affect health-related quality-of-life. Hot flash symptoms in patients with breast cancer can be treated similarly to those experienced by other patients. Agents often used include antidepressants such as fluoxetine and venlafaxine, both of which come with their own side effects. [138]

Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) are both rare but are reported consequences of treatment with certain chemotherapy agents (e.g., alkylating agents and topoisomerase II inhibitors). Leukemia can present as soon as six months after the conclusion of therapy with reports of AML up to five years post chemotherapy. Patients with MDS usually present between five and seven years after the conclusion of therapy. Risk of both AML and MDS appears to be dose dependent, and women who receive an anthracycline-based regimen appear at greater risk than those who receive standard dose CMF. [139]

Other effects that are more anecdotal and not well documented are cognitive impairment, weight gain, and depression. Cognitive impairment has been reported in a number of smaller trials; however, because of differing methodology and assessment techniques, estimating an actual incidence or risk factors for developing cognitive

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[137] Burstein and Winer, "Primary Care for Survivors of Breast Cancer."

[138] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

[139] Ibid.; Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

impairment is difficult.[140] Weight gain is common in women receiving adjuvant chemotherapy. The mechanism is not known but it has been shown not to be the result of excess caloric intake, although, the gain is from fat weight alone without proportional gain in lean body mass (sarcopenic obesity). It has been suggested that this may be due to decreased physical activity. [141]

Side effects of endocrine therapies vary depending on the specific agent given. Tamoxifen usage has a number of side effects that are attributed to a mixed estrogen agonist/antagonist activity. These include menopausal symptoms (night sweats, hot flashes, vaginal dryness, and irregular menses), thromboembolic events (DVT), thrombocytopenia or leucopenia, ocular toxicity, risk of endometrial cancer, and risk of teratogenicity. Although there is an increase in risk in endometrial cancer with tamoxifen use, the risk is half when compared to the absolute decrease in contralateral breast cancer. [142]

Aromatase inhibitors have several side effects in common with tamoxifen, however, in lower frequencies. Those include hot flashes, venous thromboembolic events, endometrial cancer and vaginal bleeding. Anastrazole does have additional side effects, those include: increased rate of bone fractures, development of benign ovarian pathologies, osteoporosis and musculoskeletal symptoms. [143]

Targeted agents are used in specific patients with breast cancer based on specific genetic parameters. Trastuzumab adverse effects include infusion reactions (fever, chills,

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[140] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors."

[141] Ibid.; Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

[142] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors"; Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

[143] Hurria and Hudis, "Follow-up Care of Breast Cancer Survivors"; Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

rash), headache, diarrhea and cardiac toxicity. Infusion reactions are usually prevented

with pre-treatment with corticosteroids and antihistamines. [144]

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[144] C. Vogel et al., "First-line, Single-agent Herceptin® (trastuzumab) in Metastatic
Breast Cancer: a Preliminary Report," *European Journal of Cancer* 37, no. Supplement 1
(January 2001): 25–29.

Table 1.17 Common Consequences of Systemic Breast Cancer Therapy with Corresponding Risk Factors and Interventions [145]

Symptom	Risk Factors	Screening	Interventions
Hot Flashes	Chemotherapy, Menopause, or use of Tamoxifen or Aromatase Inhibitors	History	SSRI SNRI Gabapentin
Sexual Dysfunction	Chemotherapy, Menopause or Altered Body Image Secondary to Surgery/Radiation	History	Counseling Non-Hormonal Products for Dyspareunia
Arthralgias or MS Symptoms	Tamoxifen or Aromatase Inhibitors	History	APAP NSAIDS
Cognitive Dysfunction	Chemotherapy, Tamoxifen or Aromatase Inhibitors	History	If Progressive, Evaluate for Alzheimer's Disease
Fatigue	Chemotherapy, Tamoxifen or Aromatase Inhibitors	History	Rule-Out or Treat Psychiatric or Biologic Cause (Depression, Anemia, Hypothyroidism)
Weight Gain	Tamoxifen or Aromatase Inhibitors	History	Usual Management
Osteoporosis/Osteopenia	Chemotherapy- Induced Menopause, Tamoxifen or Aromatase Inhibitors	Bone Density Testing Prior to Initiation and Every 1 - 2 Years Thereafter	Usual Management
Thromboembolic Events	Treatment with Tamoxifen	History	No Proven Prophylaxis, Appropriate Medical Management if Present

SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; APAP: Acetaminophen; NSAIDS: Non-Steroidal Anti-Inflammatory Drugs; MS: Musculoskeletal

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[145] Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

1.3.11 OUTCOMES/MORTALITY/ PROGNOSIS

Breast cancer is the second most deadly cancer in women (second to lung cancer); however, with increased screening, which had led to earlier diagnosis, mortality is decreasing. [146] The overall five-year survival for women with cancer of any type is 80%; in contrast, 88% of women with breast cancer will survive ten years or more. [147] The clinical course of breast cancer varies widely between patients, so the prognosis of patients is an important part of the decision-making process regarding therapeutic options.

There have been several prognostic or predictive factors that have been identified; these are useful in determining outcomes such as recurrence or death, and can give information about how well patients will respond to specific therapies. [148] There are predictive and prognostic factors in each of three categories which are patient characteristics, disease characteristics, and biomarkers. These can include location of the tumor and how far it has spread, hormone receptor status, tumor markers, gene expression, tumor size and shape, and rate of cell division. [149] Disease characteristics that affect prognosis include tumor size, lymph node status, histological subtype, nuclear or histologic grade, lymphatic or vascular invasion, and proliferation indices. Both the

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[146] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

[147] Horner et al., "SEER Cancer Statistics Review 1975-2006."

[148] Avina [1] Kapoor and Victor G Vogel, "Prognostic Factors for Breast Cancer and Their Use in the Clinical Setting," *Expert Review of Anticancer Therapy* 5 (April 2005): 269–281.

[149] G. Rennert et al., "Clinical Outcomes of Breast Cancer in Carriers of BRCA1 and BRCA2 Mutations," *New England Journal of Medicine* 357, no. 2 (2007): 115.

number of lymph nodes involved and size of tumor are directly associated with prognosis. [150]

Table 1.18 Breast Cancer Five-Year Survival Rates (%) Based on Tumor Size and Axillary Lymph Node Status[151]

Tumor Size:	< 2cm	2 - 5cm	> 5cm
Negative	96	89	82
1 – 3 Positive	87	80	73
≥ 4 Positive	66	59	46

cm: centimeter

Patient-related factors are independent of disease. Those affecting prognosis include age and race. Younger patients, especially those under the age of 35, typically present with more aggressive disease and have a poorer prognosis. African-American women have a higher mortality when compared to whites, which is usually attributed to decreased access to care, resulting in presentation at a more advanced disease stage, which subsequently affects the success of treatment. Additionally, black, American-Indian, or Hispanic women are often diagnosed with more advanced disease which also has a negative effect on mortality. [152]

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[150] R.S. Rampaul et al., "Prognostic and Predictive Factors in Primary Breast Cancer and Their Role in Patient Management: The Nottingham Breast Team," *European Journal of Surgical Oncology* 27 (2001): 229–238.

[151] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

[152] Christopher I. Li, Kathleen E. Malone, and Janet R. Daling, "Differences in Breast Cancer Stage, Treatment, and Survival by Race and Ethnicity," *Arch Intern Med* 163, no. 1 (January 13, 2003): 49–56.

Table 1.19 Breast Cancer Mortality Rates in Females by Race from 2002 to 2006[153]

Race/Ethnicity	Rate*
All	24.5
White	23.9
Black	33.0
Asian/Pacific Islander	12.5
American Indian/Alaska Native	17.6
Hispanic	15.5

*Rate is per 100,000 Women

Table 1.20 Five-Year Relative Survival Rate by Estimated Stages at Diagnosis [154]

Stage	Percentage of Cases	5-Year Survival
Localized (I and II)	60	98.3
Regional (II and III)	33	83.5
Distant (IV)	5	23.3
Un-Staged	2	57.7

[153] Horner et al., "SEER Cancer Statistics Review 1975-2006."
[154] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

Hormone receptor status is not thought of as a prognostic factor, but usually, this is used for gauging response to hormone manipulation therapy, therefore is indirectly related to prognosis. Approximately 75% of breast cancer tumors are estrogen receptor positive, and about 65% of these are progesterone receptor positive. Cells that are positive to either one or both are considered hormone-receptor positive. If tumors are hormone-receptor positive, they are considered hormone sensitive since they respond to hormone therapy. Women with hormone-sensitive tumors have a better prognosis because these tumors grow more slowly than hormone-receptor negative tumors. The largest decline in mortality rates are seen in women with HR positive tumors due to the addition of hormone therapy. [155] HER-2 over-expression, in contrast to hormone receptor status, does give an indication of prognosis. HER-2 is often associated with more aggressive disease, higher rates of recurrence and mortality. [156]

Overall, lymph node status and tumor size are the two most important prognostic and predictive factors to assist in therapy decisions. There are computer-aided models (e.g., adjuvantonline.com) that can incorporate the individual factors with tumor related variables to assist in predicting prognosis and help in the selection of therapy for early stage disease. [157]

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[155] Donald A. Berry et al., "Estrogen-receptor Status and Outcomes of Modern Chemotherapy for Patients with Node-positive Breast Cancer," *Journal of the American Medical Association* 295, no. 14 (2006): 1658.

[156] Brian Leyland-Jones, "Trastuzumab: Hopes and Realities," *The Lancet Oncology* 3, no. 3 (March 2002): 137–144; Jeffrey S. Ross, "Multigene Classifiers, Prognostic Factors, and Predictors of Breast Cancer Clinical Outcome," *Advances in Anatomic Pathology* 16, no. 4 (2009): 204–215.

[157] M. Cianfrocca and L. J Goldstein, "Prognostic and Predictive Factors in Early-stage Breast Cancer," *The Oncologist* 9, no. 6 (2004): 606.

1.4 Heart Failure

Generally speaking, heart failure is a clinical syndrome in which the heart is unable to pump a sufficient amount of blood to the rest of the body to meet metabolic needs. This can result from any condition that reduces ventricular filling or myocardial contractility (ventricle is either unable to fill with or pump blood), however common causes are hypertension and coronary artery disease. Therefore, heart failure can be considered an end to a number of pathways from other cardiac disorders that affect valves, pericardium and myocardium. Heart failure can result from any disorder that affects the heart's ability to contract or relax, and these can be disruptions of filling, contraction or both. The syndrome is progressive and its primary symptoms include dyspnea, fatigue and fluid retention. [158]

1.4.1 DISEASE PROCESS

Heart failure usually begins with a myocardial injury; this can be an acute event such as a myocardial infarction or could be the result of a chronic disorder such long-term uncontrolled hypertension. Whether acute or chronic, the decreases in cardiac output causes activation of compensatory mechanisms, which attempt to maintain normal cardiac output. One compensatory mechanism includes activation of the sympathetic nervous system and this is meant to increase heart rate and contractility. Additionally, the Frank-Starling mechanism compensates for decreased cardiac output by increasing stroke volume. The increased stroke volume results in vasoconstriction and ventricular

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[158] Barry M. Massie, "Heart Failure: Pathophysiology and Diagnosis," in *Goldman: Cecil Medicine* (Philadelphia: Saunders Elsevier, 2011), Chapter 58, http://www.mdconsult.com.ezproxy.lib.utexas.edu/.

hypertrophy, subsequently leading to cardiac remodeling. The compensation is meant to be short term; however, the sustained activation of these systems is what causes the progression of the disease. [159]

The signs and symptoms of heart failure are a result of the activation of all of the compensatory mechanisms. However, ventricular hypertrophy and remodeling are considered the cause of disease progression. Ventricular hypertrophy basically means that there is increased muscle mass and remodeling refers to alterations in cellular structure of the myocardial and extracellular matrix which result in changes to size, shape, structure and function of the heart. This occurs as a result of any condition that can cause myocardial injury including, but not limited to, myocardial infarction, hypertension, valvular disease and cardiomyopathy. Remodeling starts before the manifestation of symptoms, it continues after symptoms develop, and usually is responsible for the progression of symptoms. [160]

Remodeling occurs at many levels in the heart and is an extremely complex process (Figure 1.1) The progression of the process leads to additional compensation, which results in greater reductions in myocardial systolic and diastolic dysfunction, which causes greater injury, which leads to further compensatory activation. Systemic and local release of endogenous neurohormones such as vasopressin, norepinephrine, angiotensin II, aldosterone, and pro-inflammatory cytokines are considered the key elements in the ventricular remodeling process. [161]

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[159] Paresh A Mehta and Martin R Cowie, "Epidemiology and Pathophysiology of Heart Failure," *Medicine* 34, no. 6 (June 1, 2006): 210–214.

[160] Gary S. Francis et al., "Pathophysiology of Heart Failure," in *Hurst's the Heart*, 12th ed. (New York: McGraw-Hill Medical, 2008), Chapter 24; Henry Krum and William T Abraham, "Heart Failure," *The Lancet* 373, no. 9667 (March 14, 2009): 941–955.

[161] Francis et al., "Pathophysiology of Heart Failure"; Robert B. Parker, Jo E. Rodgers, and Larissa H. Cavallari, "Chapter 16: Heart Failure," in *Pharmacotherapy: A Pathophysiologic Approach*, ed. Joseph T.

Figure 1.1 Components of Cardiac Remodeling[162]

LV=Left Ventricle
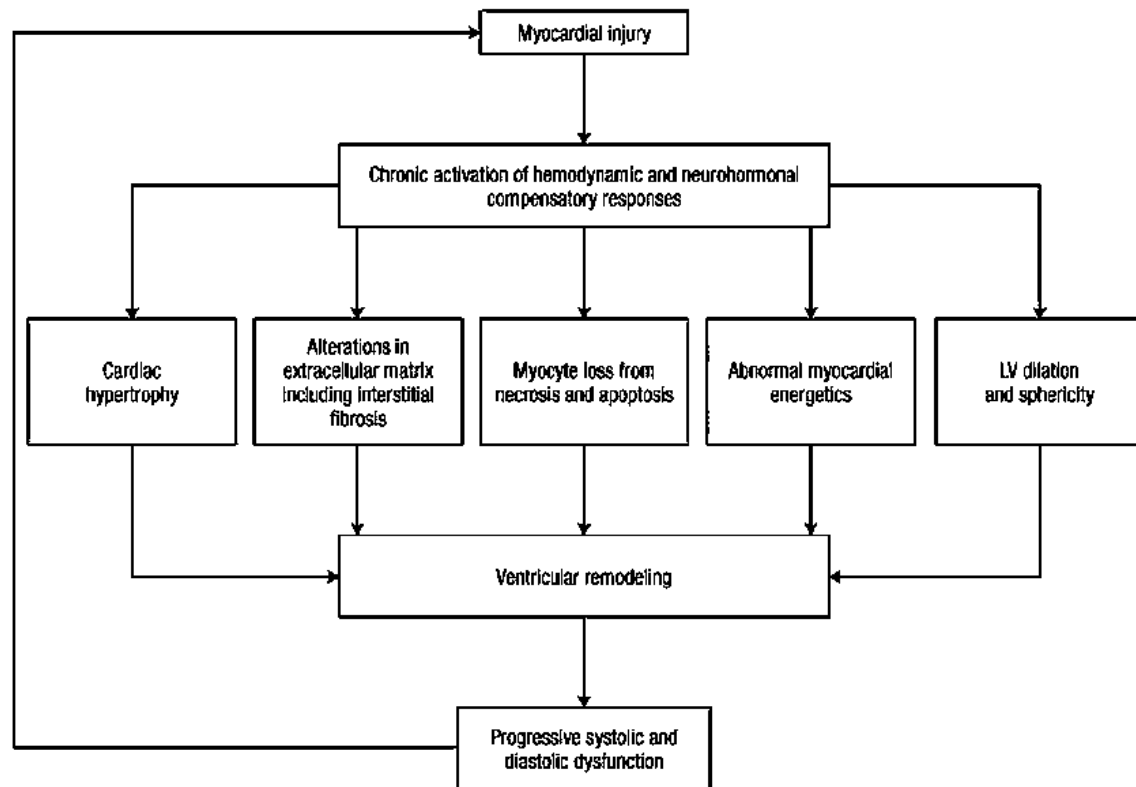
Dipiro et al., 7th ed. (McGraw-Hill Medical, 2008),
http://www.accesspharmacy.com.ezproxy.lib.utexas.edu/content.aspx?aID=3189946.
[162] Parker, Rodgers, and Cavallari, "Chapter 16: Heart Failure."

1.4.2 CLASSIFICATION

Heart failure is a progressive condition and there are a number of classification systems that outline this progression, these typically begin with risk factors and progress through worsening of symptoms. The American College of Cardiology (ACC) and the American Heart Association (AHA) have a grading system with four stages progressing from A to D. [163] These illustrate the progression of disease from risk factors to end-stage refractory disease. In contrast, the New York Heart Association (NYHA) has a classification system that is widely used and familiar to most clinicians. The NYHA classification essentially stratifies patients on their functional ability or level of symptoms. [164] Similar to the ACC/AHA system there are four categories from ranging from I to IV. The ACC/AHA classification is meant to supplement, not replace the NYHA heart failure classification. Since the NYHA classification is based on symptoms, patients in all four NYHA functional classes would correspond to ACC/AHA Stage C or D. [165]

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[163] Sharon Ann Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation," *Journal of the American College of Cardiology* 53, no. 15 (2009): e1–e90.

[164] Claiborne Miller-Davis, Sue Marden, and Nancy Kline Leidy, "The New York Heart Association Classes and Functional Status: What Are We Really Measuring?," *Heart & Lung: The Journal of Acute and Critical Care* 35, no. 4 (2006): 217–224.

[165] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

Table 1.21 ACC/AHA Heart Failure Classifications [166]

Stage	Characteristics
A	High risk for heart failure without structural heart disease or symptoms
B	Heart disease with asymptomatic decrease in left ventricular ejection fraction
C	Prior or recurrent symptoms of heart failure
D	Refractory end stage heart failure

ACC: American College of Cardiology; AHA: American Heart Association

Table 1.22 NYHA Heart Failure Classifications [167]

Class	Symptoms
I	Patients with cardiac disease but without limitations of physical activity, ordinary physical activity does not cause dyspnea, fatigue, or palpitations
II	Patients with cardiac disease that results in slight limitations of physical activity, ordinary physical activity results in dyspnea, fatigue, palpitations or angina
III	Patients with cardiac disease that results in large marked limitation of physical activity, although patients are comfortable at rest, less than ordinary will lead to symptoms
IV	Patients with cardiac disease that results in the inability to carry on physical activity without discomfort, symptoms of heart failure are present at rest, with any level of physical activity symptoms is experienced

NYHA: New York Heart Association

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166 Ibid.

167 Miller-Davis, Marden, and Leidy, "The New York Heart Association Classes and Functional Status: What Are We Really Measuring?".

1.4.3 TREATMENT

Treatment choices often depend on the etiology and stage. (Figure 1.2) Prior to initiation of drug therapy, it is important to remove any precipitating factors and identify risk factors. Those with causes such as hyperthyroidism, often do not need traditional heart failure therapies after the underlying condition is resolved. Similarly, those patients with correctible mechanical issues such as valvular disorders can often have heart failure corrected with valve replacement surgery, if diagnosed early enough.

Figure 1.2 Stages and Corresponding Interventions in the Development of Heart Failure[168]
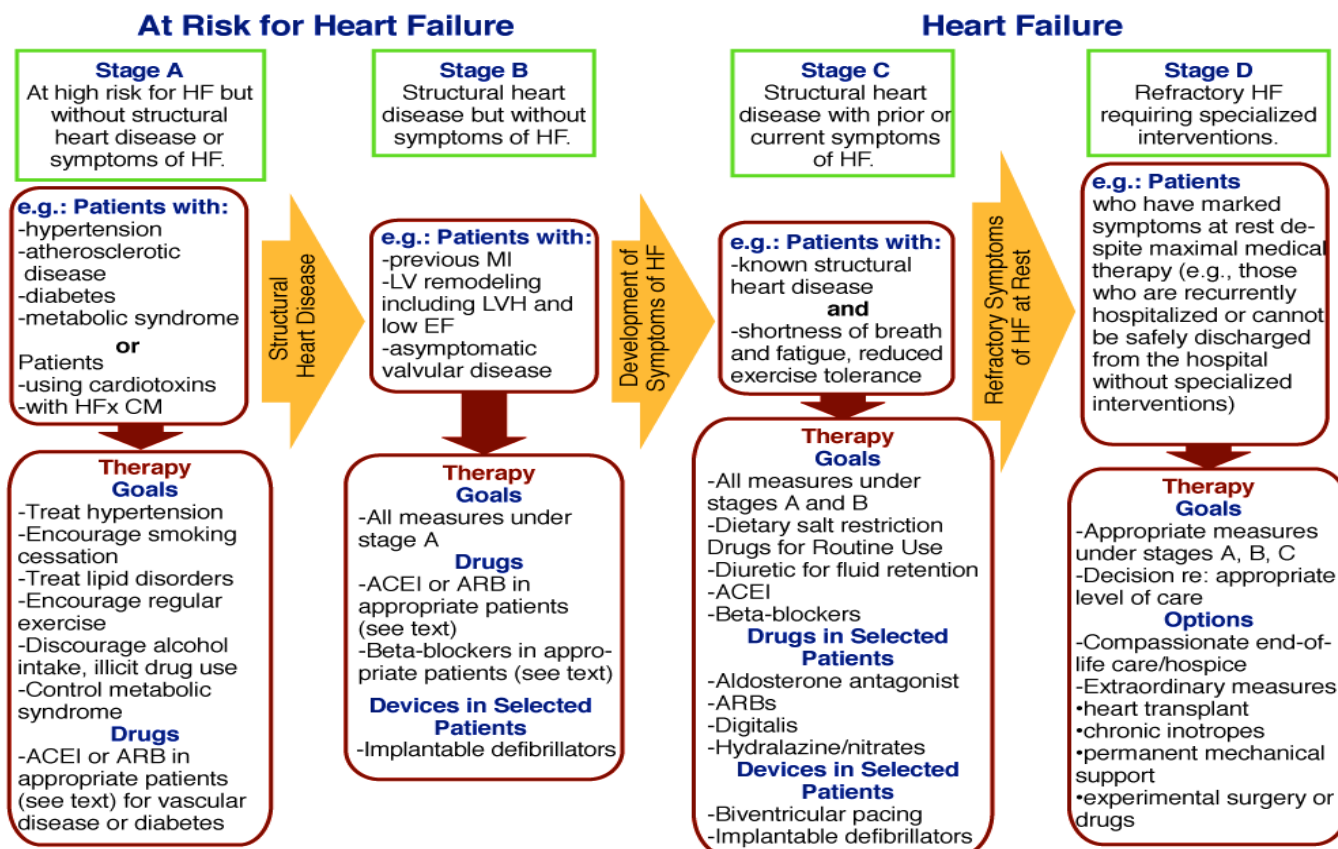
168 Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

Symptomatic improvement is seen with the use of diuretics to decrease the volume overload, and nitrates, hydralazine or calcium channel blockers to reduce angina. Remodeling is addressed at a number of junctures in the pathway with the use of angiotensin-receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACE inhibitors), beta blockers, aldosterone receptor antagonists and digoxin (use of digoxin, although historically important, has fallen out of favor because of the substantial number of drug interactions, risk of toxicity and lack of mortality benefit). Each medication has specific indications for use, as well as contraindications, according to available published guidelines. Therapy needs to be individualized for each patient. Although use of these therapies has been shown to slightly decrease mortality and improve symptoms, progression of disease is inevitable. In patients with refractory disease, transplantation or mechanical circulatory assist devices (e.g., LVAD, left ventricular assist device) may be considered. LVAD therapy is occasionally used as a type of bridge to transplantation. The indications for cardiac transplantation are listed in Table 1.23. [169]

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[169] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline," *Journal of Cardiac Failure* 16, no. 6 (June 2010): e1–e194.

Table 1.23 Indications for Cardiac Transplantation Stratified by Levels of Evidence[170]

Absolute
For Hemodynamic compromise due to HF
Refractory Cardiogenic Shock Documented dependence on IV Inotropic support to maintain adequate organ perfusion Peak VO$_2$ less than 10 mL per kg per minute with achievement of anaerobic metabolism
Severe symptoms of ischemia that consistently limit routine activity and are not amenable to CABG or PCI
Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities
Relative
Peak VO$_2$ 11-14 mL per kg per minute (or 55% of predicted) and major limitations of ADL's
Recurrent unstable ischemia not amenable to other intervention
Recurrent instability of fluid balance or renal function not due to patient non-compliance with medication regimen
Insufficient
Low LVEF
History of NYHA Functional Class III or IV symptoms
Peak VO$_2$ greater than 15 mL per kg per minute (and greater than 55% predicted without other indications)

HF: Heart Failure; IV: Intravenous; kg: kilogram; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention;
ADL's: Activities of Daily Living

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[170] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

Therapy goals and choices in medications are aimed at decreasing symptoms, reversing the ventricular remodeling process and controlling co-morbid conditions such as hypertension, diabetes, angina and arrhythmias. (Table 1.24) [171]

Table 1.24 Treatment Objectives for Chronic Heart Failure[172]

Goal	Potential Outcomes
Improve Prognosis	Reduction in Mortality
Reduce Morbidity	Relieve Signs and Symptoms
	Improve Quality of Life
	Eliminate edema and fluid retention
	Increase exercise capacity
	Reduce Fatigue and Breathlessness
	Reduce Need for Hospitalizations
	Provide for end of life care
Increase Prevention	Decrease Occurrence of Myocardial Damage
	Prevent Progression of Myocardial Damage
	Reverse Remodeling of the Myocardium
	Decrease Reoccurrence of symptoms and fluid accumulation
	Hospitalization

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[171] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline"; Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

[172] Kenneth Dickstein et al., "ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008," *European Journal of Heart Failure* 10, no. 10 (October 1, 2008): 933 –989.

1.4.4 OUTCOMES/ ASSESSMENT OF THERAPY

There are three main monitoring parameters needed in the ongoing assessment of heart failure patients. Those include periodic monitoring of 1) functional capacity, 2) volume status and 3) laboratory evaluations. Functional capacity is usually determined by the reporting of the presence and severity of symptoms by the patient. When assessing patient reports of symptoms it is important to ask specific pointed questions regarding what symptoms they are experiencing (i.e., "are you experiencing shortness of breath") as opposed to asking in general, if they are/are not experiencing symptoms. [173]

Volume status is controlled by the appropriate use of diuretic therapy and directly affects the hallmark signs and symptoms of heart failure. There are objective measures performed during a routine physical exam that can be used to assess volume status, those measures include: patient weight, jugular venous distention (JVD), presence of hepatojugular reflex, presence of pulmonary congestion and peripheral edema. Symptoms suggestive of volume overload include increasing dyspnea with or without exertion, nocturia, and paroxysmal nocturnal dyspnea. Blood pressure is an indirect indicator of volume overload and should be monitored in patients with or without underlying hypertension. [174]

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[173] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline."

[174] Robert C. Hendel et al., "ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine Endorsed by the American College of Emergency Physicians," *Journal Of The American College Of Cardiology* 53, no. 23 (June 9, 2009): 2201–2229; Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

Laboratory monitoring should include regular serum electrolytes and renal function (including BUN). Elevated potassium levels may occur with the use of aldosterone receptor antagonists, ACE inhibitors and ARBs, which subsequently can predispose patients on digoxin to toxicity. Renal function is an additional monitoring parameter important in diuretic use and can be used indirectly to assess the efficacy of ACE inhibitors or ARBs, which are often used to preserve renal function.[175]

Table 1.25 Important Assessment Criteria During Routine Follow-Up[176]

Clinical Parameters	Educational Parameters
Functional Capacity and Activity Level	Patient's Understanding of/Compliance with Dietary Sodium Restriction
Changes in Body Weight	Patient's Understanding of/Compliance with Medication Regimen
History of arrhythmia, syncope, pre-syncope, palpitations	Adherence and response to therapeutic interventions
The presence or absence of exacerbating factors for HF	

HF: Heart Failure

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[175] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline"; W.H. Wilson Tang et al., "National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure," *Clinical Biochemistry* 41, no. 4–5 (March 2008): 210–221.

[176] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline."

1.4.5 PROGNOSIS

Heart failure is usually associated with a disease course that involves frequent hospitalizations (risk for readmission is highest immediately following prior admission), poor prognosis, a complex medication regimen and diminished quality of life. Because HF is a syndrome as opposed to a primary diagnosis, there are often co-morbid conditions that can complicate treatment, or worsen prognosis, even if LV dysfunction has remained clinically stable or slightly improved. Co-morbidities are extremely important to consider when treating heart failure patients, both coronary artery and diabetes are well studied co-morbidities that have been shown to increase mortality in heart failure patients. [177]

The ability to accurately predicting prognosis would not only useful to the clinician but also to patients and their caregivers, unfortunately, this is difficult and unreliable. In attempting to determine a patients prognosis one must consider disease etiology, rate of disease progression and co-morbidities. Benefits of using a prediction model could include: communicating realistic expectations to patient and/or family/caregivers regarding disease progression, goals of therapy and prognosis, assist in making decision regarding the use of devices and/or transplantation/surgical options, potentially assist in selecting therapies to positively enhance HRQOL and mortality. [178]

The flip side is that the models were developed in specific study populations and care must be taken when using to make patient level predictions- this may be difficult for providers to communicate the uncertainty involved to patients and their families and/or caregivers, patient specific behaviors like regimen compliance, preference and patient

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[177] Ibid.

[178] Lee R Goldberg and Mariell Jessup, "A Time to Be Born and a Time to Die," *Circulation* 116, no. 4 (2007): 360–362.

attitudes are not incorporated, as newer therapies become available-models may become obsolete. [179]

Models are meant as a supplement, and never a replacement for the judgment of the specialist or management team. [180] From the available models, there have been a number of variables that can be used as surrogates to assist in predicting prognosis. Variables that have been described as correlating with prognosis include progressing NYHA functional status; decreasing LVEF, anemia, and resistance to therapy (Table 1.26) [181] High levels of circulating neurohormones (norepinephrine and endothelin) are highly correlated with increased mortality; however, they are not easily measured and are more applicable to the research setting. [182]

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[179] Ibid.

[180] Ibid.

[181] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline"; Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

[182] Jay Cohn et al., "Unconventional End Points in Cardiovascular Clinical Trials: Should We Be Moving Away From Morbidity and Mortality?," *Journal of Cardiac Failure* 15, no. 3 (April 2009): 199–205.

Table 1.26 Key Prognostic Parameters and Mode of Assessment in Heart Failure [183]

Subjective	Physical Exam	Objective Laboratory Tests	Other Tests
Worsening NYHA Functional Status	Chronic Hypotension	Degree of Hyponatremia	Decreasing LVEF
Intolerance to Conventional Therapy	Resting Tachycardia	Decreasing Hematocrit	Widened QRS
Refractory Volume Overload		Renal Insufficiency	Decreasing Exercise Peak Oxygen Uptake

NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction

There are a number of examples of prediction models that can be used in patients with heart failure. Models commonly seen in the literature include The Effect Model (also known as the Heart Failure Risk Scoring System), The Seattle Heart failure model (SHFM), and the Heart Failure Survival Score (HFSS). When using models, clinicians must remember that these variables were derived statistically from larger heart failure populations, which may have included specifically recruited study participants, and must use care in using these to predict outcomes for individual patients. [184]

The EFFECT Model (or heart failure risk scoring system) was developed from a population of hospitalized patients and its use is intended as such. This model uses a number of variables to predict 30-day and one-year mortality. Those include both heart failure related and co-morbidity data. Each predictor is assigned points and points are then summed. The sum corresponds to categories of risk that range from "very low"

[183] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline."

[184] A.L. Nutter, T. Tanawuttiwat, and M.A. Silver, "Evaluation of Six Prognostic Models in 80 Heart Failure Patients with a Fatal Heart Failure Admission," *The Journal of Heart and Lung Transplantation* 28, no. 2, Supplement 1 (February 2009): S140.

(< 60 points) to "very high" (> 150 points). There is an online calculator for the Effect Model available at www.ccort.ca/CHFriskmodel.aspx that is supported by the Canadian Cardiovascular Outcomes Research Team (CCORT). When using the online calculator, the user needs to select whether they are using U.S. or S.I. units, enters the patients age, RR and SBP at presentation, BUN, whether serum sodium is < 136 mEq/L (yes or no), select whether there are co-morbidities present such as dementia, cerebrovascular disease, malignancy, COPD, anemia, or hepatic cirrhosis. Once calculated the uses then refers to the corresponding tables for 30-day and one-year risk. [185]

The Heart Failure Survival Score was developed and validated in ambulatory patients, all of which were in NYHA stages III or IV and being considered for cardiac transplantation. Variables used to derive the score include LVEF, peak VO_2, resting HR, mean arterial blood pressure, presence or absence of CAD, presence or absence of interventricular conduction delay on ECG, and serum sodium (there is an invasive version that includes PCWP in the calculation). The sum is multiplied by a defined coefficient and the result ranks patients into low, medium and high risk categories. The HFSS was meant to assist in selecting patients for transplant; however, it was developed long before many current therapies were developed that improve survival. [186]

The Seattle Heart Failure Model (SHFM) has benefits over the previous two models in that is was developed and validated in a broader population and includes more readily available variables such as medications and devices. The SHFM is available online for use by healthcare professionals (www.seattleheartfailuremodel.org). The user enters baseline demographics of the patient such as age, gender, NYHA functional class,

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[185] Ibid.

[186] Keith D. Aaronson et al., "Development and Prospective Validation of a Clinical Index to Predict Survival in Ambulatory Patients Referred for Cardiac Transplant Evaluation," *Circulation* 95, no. 12 (June 17, 1997): 2660 –2667.

weight, systolic blood pressure, ejection fraction. There are check boxes to indicate whether the patient has HF due to ischemic causes, which medication classes they are receiving, whether they have a prolonged QRS interval and whether they have any devices placed. There are also fields to enter particular lab values of interest such as H/H, uric acid, sodium, total cholesterol and lymphocytes and if the patient is taking a diuretic, the particular dose they are receiving. This calculator can also estimate potential gains from adding additional interventions (i.e. adding an ARB to existing ACE inhibitor therapy. [187]

1.4.6   MORTALITY

Mortality due to heart failure after the onset of symptoms is extremely high, although there is a range of actual number reported which usually differ based on the baseline characteristics of the study population and medications under study. Data from the Framingham study have demonstrated that there has been a slight decline in mortality from heart failure. The one-year mortality decreased from 30% to 28% in men and from 28% to 24% in women. This decline was seen from data collection periods which included 1950-1969 and 1990-1999. [188] The five-year mortality decreased from 70% to 59% and 57% to 45% in men and women respectively. The overall trend demonstrates a

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[187] W.C. Levy, D. Mozaffarian, and D.T. Linker, "Seattle Heart Failure Model - an Individualized Prediction of Mortality," *The Journal of Heart and Lung Transplantation* 25, no. 2, Supplement 1 (February 2006): S55; Wayne C Levy et al., "The Seattle Heart Failure Model: Prediction of Survival in Heart Failure," *Circulation* 113, no. 11 (2006): 1424–1433.

[188] Lesley H Curtis et al., "Early and Long-term Outcomes of Heart Failure in Elderly Persons, 2001-2005," *Arch Intern Med* 168, no. 22 (2008): 2481–2488.

mortality decrease of approximately 12% per decade, while most of the decline was seen after 1980; almost all of it was after 1990.[189]

There was a consistent change in mortality seen in a similar study conducted by the Mayo Clinic. The data collection periods for the Rochester study included 1979 to 1984 and 1996 to 2000. Mayo observed decreases in one-year mortality of 30% to 21% and 20% to 17% in men and women respectively. Five year mortality showed a similar trend 65% to 50% and 51% to 46% in men and women respectively, improving most in younger men and least in older women. [190] Contributions to the change in mortality (and reduction in hospitalizations) are attributed to advances in drug therapy, increase in specialist/sub-specialist care and multi-disciplinary management. [191]

Drug therapy has been given partial credit for improvement in heart failure mortality. Drug classes that have been shown to improve mortality in heart failure patients include ACE inhibitors, ARB's, beta blockers and aldosterone antagonists. These therapeutic advances in addition to newer medications for treatment of co-morbid conditions (such as statins for hypercholesterolemia) and those that treat conditions considered as risk factors (medications for better blood pressure control) contribute to a slight decline in mortality. [192]

There are non-modifiable patient-related factors that contribute to mortality. These include age and gender. There are a number of studies that demonstrate a positive correlation between age and mortality. Although, there is an increase in mortality as patients' age, the Framingham investigators did note that mortality in advanced age

[189] Ibid.

[190] Daniel Levy et al., "Long-Term Trends in the Incidence of and Survival with Heart Failure," *N Engl J Med* 347, no. 18 (2002): 1397–1402.

[191] Ibid.

[192] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline."

groups decreased between the two observation periods. Patients between the ages of 65 and 74, who survived at least 30 days after disease onset, saw a mortality decrease from 66 to 54% and 47 to 40% in men and women respectively. [193] These results also show a lower mortality for women than men, which is consistent with the results seen in the Mayo study and a number of other trials.[194][195] A pooled analysis of five trials sought to examine specifically if there were survival differences between genders reported an overall hazard ratio for women of 0.77 when compare to men. [196]

Ultimately, sudden cardiac death or progressive decompensation of heart failure is the reported cause of death in heart failure patients. [197] Although some may argue that distinction is difficult, heart failure trials often have differing criteria on how they define cardiac death as sudden or progressive. [198] A proposed standardized classification system called ACME was developed in response to inconsistent reporting of the cause of death in heart failure patients. ACME stands for activity, cause, mode and event. These authors propose that if a more precise cause of death is known, more productive research can be conducted for prevention, although the progressive versus sudden death remain the convention.[199]

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[193] Curtis et al., "Early and Long-term Outcomes of Heart Failure in Elderly Persons, 2001-2005."

[194] Ibid.

[195] Levy et al., "Long-Term Trends in the Incidence of and Survival with Heart Failure."

[196] Camille G. Frazier et al., "Associations of Gender and Etiology With Outcomes in Heart Failure With Systolic Dysfunction: A Pooled Analysis of 5 Randomized Control Trials," *Journal of the American College of Cardiology* 49, no. 13 (April 3, 2007): 1450–1458.

[197] Heart Failure Society of America, "HFSA 2010 Comprehensive Heart Failure Practice Guideline."

[198] R. Narang et al., "Mode of Death in Chronic Heart Failure," *European Heart Journal* 17, no. 9 (1996): 1390–1403.

[199] Ibid.

1.5 Summary of Chapter One

Breast cancer and heart failure are both complex diseases. Either disease alone has the potential for grim outcomes, for patients burdened with both conditions, outcomes are especially poor. Breast cancer, if discovered early, can be curable. In contrast, heart failure cannot. To be cured of cancer and subsequently be diagnosed with heart failure caused by the chemotherapy is a devastating consequence of treatment. The following literature reviews will examine the cardiovascular consequences of breast cancer therapy and monitoring strategies.

CHAPTER TWO: CARDIOVASCULAR COMPLICATIONS OF BREAST CANCER THERAPY

2.1 Introduction

Diagnosing patients with heart failure is an extremely complex process and trying to determine if heart failure is a consequence of cancer therapy can be even more difficult. Reasons for this include that the signs and symptoms of cardiovascular disease and cardiac-related drug toxicity are essentially indistinguishable and the cardiac effects from cancer therapies are extremely diverse. [200] Cardiac side effects that can result from chemotherapy can include arrhythmias, ischemia, peripheral vascular disease, pericardial disease and left ventricular dysfunction.[201] Each can be caused by a number of agents or combinations of agents used for a variety of tumor types. This can include treatment with chemotherapy, biological response modifiers and radiation. [202]

An additional confounding factor that makes diagnosis difficult is cardiovascular effects from cancer therapies may not become apparent until many years after treatment is concluded. This is true for both adult and childhood cancers. [203] In fact, in childhood cancers, cardiovascular effects may arise from manifestations of thyroid abnormalities, growth hormone dysregulation, obesity, pulmonary fibrosis, and renal dysfunction

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[200] Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

[201] Kesavan Shan, A. Michael Lincoff, and James B Young, "Anthracycline-Induced Cardiotoxicity," *Annals of Internal Medicine* 125, no. 1 (1996): 47–58.

[202] Ibid.; Edward T. H. Yeh and Courtney L. Bickford, "Cardiovascular Complications of Cancer Therapy: Incidence, Pathogenesis, Diagnosis, and Management," *Journal of the American College of Cardiology* 53, no. 24 (June 16, 2009): 2231–2247.

[203] S E Lipshultz et al., "Monitoring for Anthracycline Cardiotoxicity," *Pediatrics* 93, no. 3 (March 1994): 433–437; Steven E. Lipshultz et al., "Late Cardiac Effects of Doxorubicin Therapy for Acute Lymphoblastic Leukemia in Childhood," *New England Journal of Medicine* 324, no. 12 (March 21, 1991): 808–815.

resulting from cancer treatment. [204] These may present as mildly symptomatic changes in regular function such as decreased exercise tolerance and shortness of breath to overt heart failure and reduced left ventricular ejection fraction. [205]

2.2 Mechanism of Cardiotoxicity

Complex interactions occur between treatments/agents that cause damage through several different mechanisms such as ischemia, free radical myocardial damage, radiation damage, alteration in conduction, and factors that increase myocardial stress such as increased work load, wall stress and underlying ischemia. Specific mechanisms differ depending on the treatment or drug class and whether radiation therapy was received. [206]

A classification scheme was developed by Ewer and Lippman that characterizes the types of cardiac effects seen from different agents (See Figure 2.1). Types I and II, involving anthracyclines and trastuzumab respectively, are specifically relevant to cardiotoxicity from breast cancer treatment. [207]

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[204] A.S Hinkle et al., "Cardiotoxicity Related to Cancer Therapy," *Progress in Pediatric Cardiology* 8, no. 3 (January 1, 1998): 145–155.

[205] Pawan K Singal and Natasha Iliskovic, "Doxorubicin-Induced Cardiomyopathy," *N Engl J Med* 339, no. 13 (1998): 900–905.

[206] C. L. Shapiro et al., "Cardiac Effects of Adjuvant Doxorubicin and Radiation Therapy in Breast Cancer Patients," *Journal of Clinical Oncology* 16, no. 11 (1998): 3493; P. Singal et al., "Adriamycin-induced Heart Failure: Mechanisms and Modulation," *Molecular and Cellular Biochemistry* 207, no. 1 (2000): 77–86.

[207] James L. Speyer, Boris Kobrinsky, and Michael S. Ewer, "Cardiac Effects of Cancer Therapy," in *Abeloff: Abeloff's Clinical Oncology* (Philadelphia: Churchill Livingstone/Elsevier, 2008), Chapter 63, http://www.mdconsult.com.ezproxy.lib.utexas.edu/.

Figure 2.1 Types of Treatment-Induced Cardiotoxicity from Cancer Therapy [208]
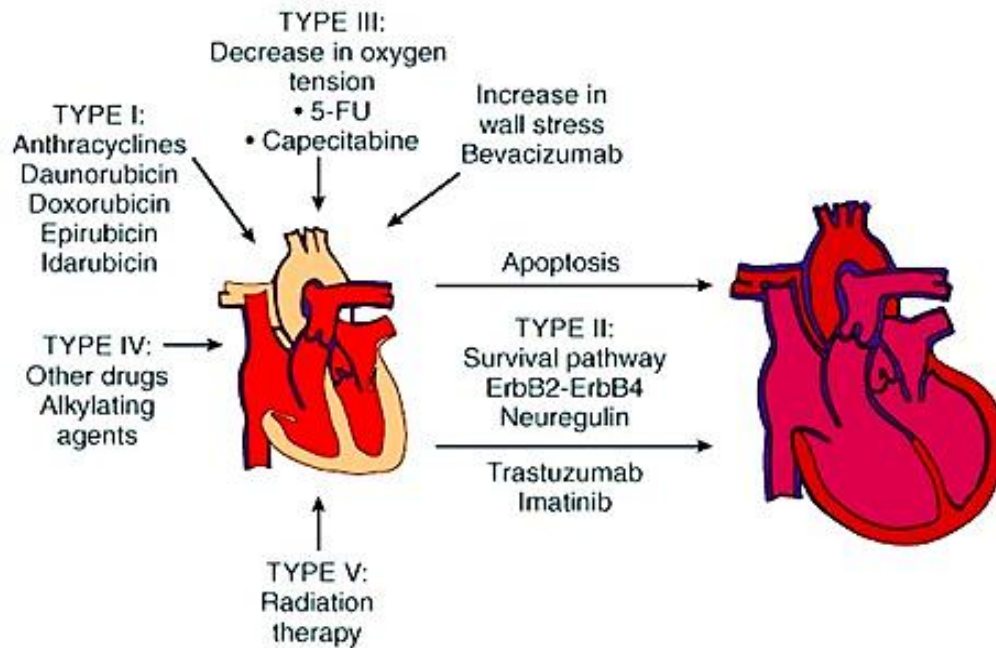
2.3 Cardiotoxicity of Specific Agents

2.3.1 ANTHRACYCLINES

For breast cancer patients that require chemotherapy for either adjuvant treatment or palliation, anthracyclines are often used. Anthracyclines are some of the most active cytotoxic agents and were discovered in the 1960's; they include doxorubicin,

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[208] Ibid.

daunorubicin, idarubicin, epirubicin and mitoxantrone. [209] Anthracyclines have three mechanisms of actions and those include: inhibiting DNA and RNA synthesis via intercalation between base-pairs preventing replication of cancer cells; inhibiting topoisomerase II, preventing the relaxation of the super coiled DNA which inhibits DNA transcription and replication; and creating iron-mediated free-oxygen radicals that damage DNA and cell membranes. (Figure 2.2) [210]

Anthracycline toxicity is a result of repeated injuries to the myocardium that gradually effect cellular defenses, damaging cells that cause myocardial wall stress and eventually leading to cell death. There are several proposed mechanisms that may lead to cardiac toxicity, including: lipid peroxidation, inhibition of nucleic acids and protein synthesis, release of vasoactive amines, changes in adrenergic function and adenylate cyclase, inhibition of spontaneous or caffeine induced sarcoplasmic reticulum calcium release, and free radical generation. [211]

Those most widely accepted mechanism is free radical generation via a reduction reaction of the drug structure with oxygen which undergoes further reduction leading to an (–OH) free radical. This can occur as either an iron dependent or iron independent reaction. If iron creates a complex with the reduced drug, this often increases the amount of cell damage. Free radicals affect cells in a number of ways; they can cause damage directly to the sarcoplasmic reticulum, DNA, mitochondria, cell membrane and nuclear envelope. Damage to the sarcoplasmic reticulum can cause an increase in free calcium,

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[209] Abeloff et al., "Cancer of the Breast"; G. Minotti, "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity," *Pharmacological Reviews* 56, no. 2 (2004): 185–229.

[210] Abeloff et al., "Cancer of the Breast"; Minotti, "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity"; Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[211] Singal et al., "Adriamycin-induced Heart Failure."

which in turn can damage myofibrillar elements. There are specific features that characterize cardiotoxicity of anthracyclines and those include the loss of myofibrils, dilation of the sarcoplasmic reticulum, cytoplasmic vacuolization, swelling of the mitochondria and an increased number of lysosomes. [212]

Figure 2.2 Proposed Mechanism of Anthracycline-Induced Cardiotoxicity[213]

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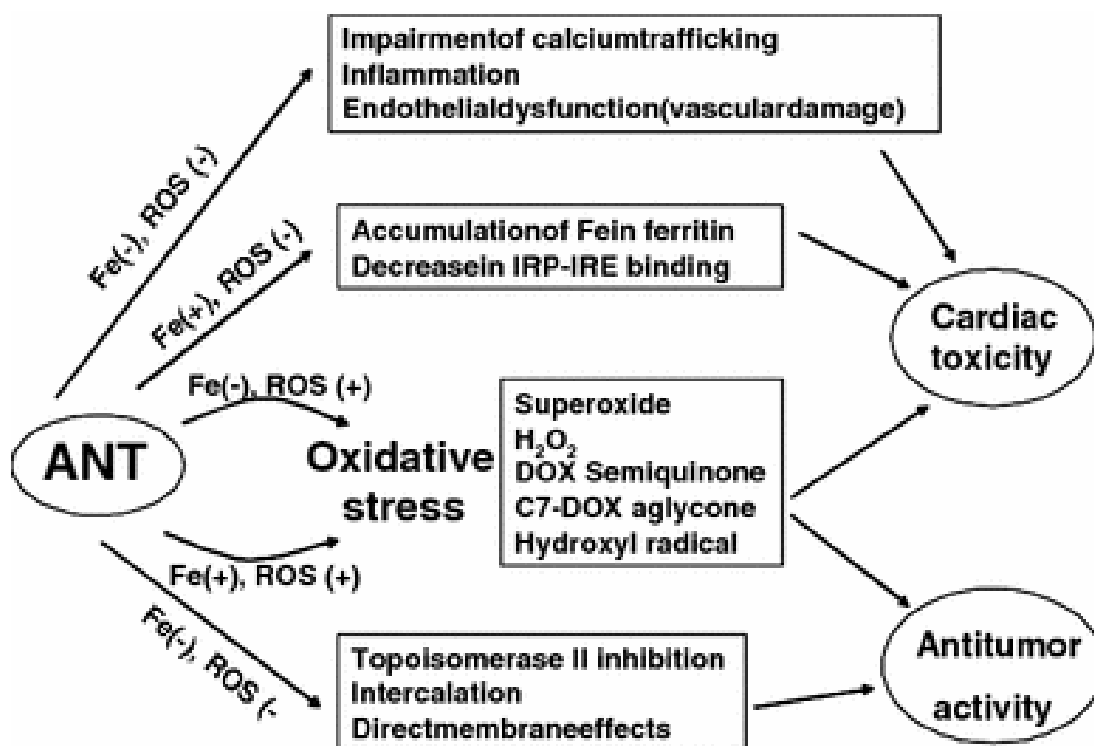
[212] Abeloff et al., "Cancer of the Breast"; Minotti, "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity"; Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[213] Helena Kaiserová et al., "New Iron Chelators in Anthracycline-induced Cardiotoxicity," *Cardiovascular Toxicology* 7, no. 2 (2007): 145–150.

2.3.2 OTHER CHEMOTHERAPY AGENTS

Anti-metabolites such as fluorouracil (5-FU), capcitabine, and fludarabine can also cause cardiotoxicity. 5-FU is widely used in a number of regimens treating a variety of different cancers; it is considered the second most common cause of chemotherapy-related cardiotoxicity after anthracylines. The proposed mechanisms include coronary artery vasospasm, myocarditis and a thrombogenic effect leading to endothelial cytotoxicity. Vasospasm is the most widely accepted mechanism. Patients present with a variety of symptoms ranging from angina, myocardial infarction and arrhythmias to acute pulmonary edema and cardiac arrest. Reported incidence ranges from 1 - 19%, but a commonly reported number is around 8%. Like anthracycline cardiotoxicity, the wide range can be attributed to the differing reporting criteria used in trials. Risk factors include the method of administration, concurrent or prior anthracycline use or radiation, and the presence of coronary artery disease. [214]

Capcitabine is an oral analog of 5-FU, with a reported incidence of cardiotoxicity that ranges between 3% and 9%. The cardiotoxic mechanism is assumed to be similar to that of 5-FU, as patients often present with similar symptoms (i.e., chest pain, MI or arrhythmias). The use of fludarabine has been associated with transient chest pain and hypotension; however, there have been seven case reports of severe cardiotoxicity when used in combination with melphalan. Nonetheless, routine use of high doses of either agent alone has not been associated with cardiotoxicity. [215]

Microtubule targeting agents, such as vinca alkaloids and taxanes, exhibit some cardiac effects. Vinca alkaloids have been implicated in a number of vaso-occluding

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[214] P Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy," *Bone Marrow Transplant* 35, no. 4 (November 15, 2004): 323–334.

[215] Yeh and Bickford, "Cardiovascular Complications of Cancer Therapy."

events such as hypertension, MI, and infarction; this is most commonly reported in vinblastine. With taxanes, paclitaxel most commonly can cause bradycardia and heart block. The use of paclitaxel or docetaxel in a breast cancer regimen is implicated in heart failure and the incidence increases up to approximately 20% when these agents are used together. It is hypothesized that taxanes potentiate the cardiotoxicity of the anthracyclines. [216]

Alkylating agents, such as cyclophosphamide, are associated with cardiomyopathy in higher dose protocols; however toxicity is not considered related to the cumulative dose administered. Platinum agents, such as cisplatin, have several cardiac effects; however, these are typically considered secondary to the renal toxicity caused by these agents. [217]

2.3.3   TRASTUZUMAB

Monoclonal antibodies and other targeted agents such as trastuzumab, rituximab, and bevacizumab have varying degrees of cardiac effects and toxicities that are related to the receptors to which they bind. Trastuzumab and bevacizumab can cause cardiomyopathy and reductions in LVEF related to cellular events arising as a function of the drug's mechanism of action. Whereas, rituximab can cause arrhythmias or angina, and this is usually considered an infusion-related reaction that is transient. [218]

The specific mechanism of trastuzumab cardiotoxicity stems from the specific inhibition of cardioprotective factors in normal repair pathways. The complex created by

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[216] Ibid.

[217] Ibid.

[218] Elizabeth L. Strevel and Lillian L. Siu, "Cardiovascular Toxicity of Molecularly Targeted Agents," *European Journal of Cancer* 45, no. Supplement 1 (2009): 318–331.

binding of the drug to the targeted receptor creates a complex that specifically inhibits cardiac repair. This complex has multiple activation steps down steam that result in hypertrophy of cardiac myocytes. [219]

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[219] Evandro de Azambuja et al., "Cardiac Toxicity with anti-HER-2 Therapies: What Have We Learned so Far?," *Targeted Oncology* 4, no. 2 (April 2009): 77–88.

Table 2.1 Classes of Chemotherapeutic Agents and Corresponding Cardiotoxic Effects [220]

Class	Agents	Cardiac Effects
Anthracyclines/ Anthraquinolones	Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone	Arrhythmias, pericarditis, myocarditis, HF, LV dysfunction
Alkylating Agents	Busulfan, Chlormethine, Cisplatin, Cyclophosphamide, Ifosfamide, Mitomycin	Endomyocardial fibrosis, pericarditis, tamponade, ischemia, MI, HTN, myocarditis, HF, arrhythmias
Anti-Metabolites	Capcitabine, 5-Fluorocuracil (5-FU), Clofarabine, Carmustine, Cytarabine	Ischemia, chest pain, myocardial infarction, HF, arrhythmias, pericardial effusions, pericarditis, hemodynamic abnormalities
Anti-Microtubule Agents	Etoposide, Teniposide, Vinca Alkaloids, Taxanes (Paclitaxel)	Hypo- or hypertension, ischemia, angina, myocardial infarction, bradycardia, arrhythmias, conduction abnormalities and HF
Biological Agents	Alemtuzumab, Bevacizumab, Cetuximab, Rituximab, Trastuzumab	Hemodynamic abnormalities, LV dysfunction, HF, thromboembolism, angioedema and arrythmias
Interleukins	Denileukin, IL-2, IFN-α	Hypotension, capillary leak syndrome, arrythmias, coronary artery thrombosis, ischemia and LV dysfunction
Tyrosine Kinase Inhibitors	Imatinib Mesylate, Sorafenib, Sunitinib, Dasatinib, Relotinib, Gefitinib, Lapatinib	HF, edema, pericardial effusion, pericarditis, hypertension, arrythmias, prolonged QT interval, ischemia, chest pain
Miscellaneous Chemotherapy Agents	Asparaginase, ATRA, Arsenic Trioxide, Pentostatin, Lenalidomide, Thalidomide	ECG changes, prolonged QT interval, torsade's de pointes, other arrythmias, ischemia, angina, MI, HF, edema, hypotension, bradycardia, thromboembolism and retinoid acid syndrome

LV: Left Ventricular, HF: Heart Failure, MI: Myocardial Infarction, HTN: Hypertension, IL: Interleukin, IFN: Interferon, ATRA: All-trans-retinoic-acid; ECG: Electrocardiogram

[220] Elly Barry et al., "Anthracycline-induced Cardiotoxicity: Course, Pathophysiology, Prevention and Management," *Expert Opinion on Pharmacotherapy* 8, no. 8 (2007): 1039–1058.

2.4 Toxicity Criteria

The most prominent guideline for evaluating toxicity to cancer treatment is the National Cancer Institute's (NCI) Common Toxicity Criteria (CTC) which lists possible toxicities and/or adverse events for each organ system. These are given a grade which ranges from zero (which usually means absent or normal function) to four. Cardiovascular toxicity is split between arrhythmias and general events. A portion of the toxicity criteria relevant to the current study is illustrated in Table 2.2. [221]

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[221] A. Trotti et al., "Common Toxicity Criteria: Version 2.0. an Improved Reference for Grading the Acute Effects of Cancer Treatment: Impact on Radiotherapy," *International Journal of Radiation Oncology* Biology* Physics* 47, no. 1 (2000): 13–47.

Table 2.2 NCI Common Toxicity Criteria (Version 2.0) [222]

Adverse Event:	Grade				
	0	**1**	**2**	**3**	**4**
LVEF	Normal	Asymptomatic decline of resting EF ≥10% but <20% of baseline; FS ≥24% but < 30%	Asymptomatic but resting EF below the LLN, or decline of EF ≥20% of baseline; FS <24%	CHF responsive to TX	Severe or refractory CHF or Condition requiring intubation
cTnI	Normal			Levels consistent with unstable angina*	Levels consistent with MI*
cTnT	Normal	≥0.03 - <0.05†	≥0.05 - <0.1†	≥0.1 - <0.2†	≥0.2†

†measured in ng/mL, * as defined by manufacturer; CHF: Congestive Heart Failure; cTnI/ cTnT: Cardiac Troponins I and T; EF: Ejection Fraction; FS: Fractional Shortening; LLN: Lower Limit of Normal; LVEF: Left-Ventricular Ejection-Fraction; MI myocardial infarction; TX: Treatment

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[222] Ibid.

The NCI also has common terminology criteria for adverse events (CTCAE), and differentiates the effect of chemotherapy on left ventricular ejection fraction (LVEF) from overt heart failure. For purposes of the CTCAE, the term adverse event refers to "any unfavorable or unintended sign, symptom or disease temporarily associated with the use of a medical treatment or procedure that may or not be considered related to that treatment or procedure". [223]

The criteria of adverse events, like that of the toxicities, list each organ system and grades events. However, in the adverse event criteria, the grades range from 1 to 5. Grade 1 is considered of mild severity, where the patient may be experiencing mild symptoms or no symptoms at all by which only an observation is made and no intervention is indicated. Grade 2 is a moderate grade where the patient may be experiencing moderate symptoms that may indicate a non-invasive intervention and there may be some limitation of age-appropriate instrumental activities of daily living. Grade 3 is severe, is not considered life threatening, but often hospitalization is required and typically patients are experiencing some limitation of self-care activities of daily living. Grade 4 is considered life threatening and Grade 5 is defined as death attributed to adverse event. The common terminology criterion for adverse events that is relevant to the current study is illustrated in Table 2.3. [224]

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[223] Ibid.
[224] Ibid.

Table 2.3 NCI Common Terminology Criteria for Reporting of Adverse Events (Version 3.0) [225]

| Adverse Event: | Grade | | | | |
	1	2	3	4	5
Heart Failure	Asymptomatic with laboratory or imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest	Life-threatening consequences	Death
Ejection Fraction	-	-	Symptomatic due to drop in ejection fraction	Refractory or poorly controlled heart failure due to drop in ejection fraction	Death

[225] A. Trotti et al., "CTCAE V3.0: Development of a Comprehensive Grading System for the Adverse Effects of Cancer Treatment," *Seminars in Radiation Oncology* 13, no. 3 (July 2003): 176–181.

2.4 Heart Failure in Breast Cancer

Dilative cardiomyopathy and CHF develop after completion of cumulative anthracycline regimens usually within a year but very late forms of cardiac dysfunction have been experienced by some patients. [226] Toxicity can manifest as either sub-clinical or clinical heart failure. Sub-clinical is detectable heart damage that does not result in any symptoms.

Three distinct types of cardiotoxicity have been described and these types are determined by the amount of time that had lapsed between drug administration and symptom development. [227] The first type includes the acute or sub-acute injury which occurs during or immediately after the infusion. This type of toxicity is rare and can result in a transient arrhythmia, pericarditis or myocarditis syndrome or acute left ventricular dysfunction. The most common manifestation of immediate toxicity is non-specific ECG repolarization abnormalities which are reported in approximately 40% of patients. [228] Symptoms resolve after discontinuation of treatment, however, some patients do suffer permanent cardiac damage, especially when higher cumulative doses are received. The second type is a chronic progressive cardiotoxicity that results in cardiomyopathy. This is the most common type of cardiotoxicity and it usually manifests within the first year after treatment has concluded. The third type is also chronic;

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[226] Minotti, "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity."

[227] Barry et al., "Anthracycline-induced Cardiotoxicity: Course, Pathophysiology, Prevention and Management."

[228] Jones, Swanton, and Ewer, "Anthracycline Cardiotoxicity."

however the onset involves the development of symptoms years to decades later (this type is most often seen in childhood cancer survivors). [229]

2.4.1 INCIDENCE/PREVALENCE

The earliest reports of doxorubicin-related cardiotoxicity are in either reviews or retrospective analyses. When the drug first was used in breast cancer; heart failure was an anecdotal finding and routine monitoring was not always conducted, which may have led to an under-reporting in earlier literature. Retrospective studies have reported a wide range of incidence values for anthracycline-induced cardiotoxicity.[230] This is primarily because reporting is not standardized. Patients tend to be monitored more closely when participating in clinical trials; however, monitoring usually consists of MUGA or ECHO, neither of which are sensitive to slight changes in cardiac function.[231] Reports of cardiotoxicity in the publications resulting from phase II or III trials is typically reserved to patients in NYHA class III or IV heart failure (i.e., patients with complaints of symptoms). Patients not participating in trials could get an ECHO or MUGA scan but usually not as frequently; barriers include the high cost and extensive resource utilization involved in radiological tests. Patients may not be monitored at all until they report symptoms requiring further investigation. [232]

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[229] Abeloff et al., "Cancer of the Breast"; Minotti, "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity"; Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[230] Barry et al., "Anthracycline-induced Cardiotoxicity: Course, Pathophysiology, Prevention and Management"; Shapiro and Recht, "Side Effects of Adjuvant Treatment of Breast Cancer."

[231] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[232] L C M Kremer et al., "Frequency and Risk Factors of Subclinical Cardiotoxicity After Anthracycline Therapy in Children: a Systematic Review," *Annals of Oncology: Official Journal of the European Society for Medical Oncology / ESMO* 13, no. 6 (June 2002): 819–829.

In a systematic review of 25 studies involving pediatric patients, there was a frequency range of 0% to 57.4% reported cases of subclinical cardiotoxicity. [233] These authors noted that of the 25 included studies, 14 had serious methodological flaws or limitations. The definition of sub-clinical cardiotoxicity used in the meta-analysis was abnormal systolic function and/or afterload judged from values of either fractional shortening, ejection fraction, velocity of fiber shortening corrected for heart rate, or the stress-velocity index (all of which were measured via ECHO or radionuclide angiography). These results illustrate that there is a lack of standardized reporting, and when sub-clinical toxicity is considered, the incidence rises dramatically. [234]

2.4.2 RISK FACTORS

The risk in anthracycline cardiotoxicity is often magnified by an overlap of anthracycline exposure and subsequent sub-clinical damage. There are both drug-related and patient-related risk factors that contribute to cardiotoxicity of cancer treatment. Drug related factors include: the dose administered at each session, the cumulative dose administered, length of infusion, the combination of drugs given, dosing schedule, and sequence of combination therapy. [235]

Patient-related factors include age (especially patients < 4 or > 70), female gender, previous therapies, underlying cardiac disease, hypertension, metabolic abnormalities, liver disease, chromosome abnormalities and hypersensitivity to drugs given. Co-morbidities and unfavorable lifestyle choices such as physical inactivity can

[233] Ibid.

[234] Ibid.

[235] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

also contribute to the potential for cardiotoxicity; these risk factors may affect therapy choices or even exclude the use of anthracyclines from treatment plans particularly in older patients. [236]

Proposed risk factors for anthracycline-induced cardiotoxicity include: higher rates of drug administration, mediastinal radiation, advanced age, younger age, female sex, pre-existing heart disease, and hypertension. [237] Although, the hypothesized risk factors that have the most evidence include cumulative dose, advancing age, and combination therapy (including sequencing of medications). [238] One of the earliest reports of cardiotoxicity was by Von Hoff and colleagues where these investigators observed an increasing incidence of CHF with increasing age and also observed a difference in cases between dosing regimens. There were fewer cases in those patients who received a single dose every week when compared with patients who either received a single dose every three weeks or three consecutive daily doses every three weeks. [239]

In a retrospective study using SEER data for patients who received anthracycline therapy, the authors found an association of CHF with advancing age, black race, other co-morbid conditions or cardiac history. This study, because of the nature of the data, had ten years of follow-up information available. However, the dose of anthracycline received was not reported, and outcomes were dependent on what was reported in the billing claims. [240]

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[236] Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy"; Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[237] Robert A. Minow et al., "Adriamycin Cardiomyopathy-risk Factors," *Cancer* 39, no. 4 (1977): 1397–1402; Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy."

[238] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[239] Daniel D Von Hoff et al., "Risk Factors for Doxorubicin-lnduced Congestive Heart Failure," *Annals of Internal Medicine* 91, no. 5 (1979): 710–717.

[240] M. C. Pinder et al., "Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer," *Journal of Clinical Oncology* 25, no. 25 (2007): 3808–3815.

Cardiac risk factors (e.g., hypertension) predispose patients to heart failure independent of receiving anthracycline therapy. Numerous studies suggest that patients with a cardiac history are at increased risk. In one study by Ryberg et al, the authors found that there was a three-fold increase in cardiotoxicity in patients with cardiac risk factors (i.e., hypertension, diabetes, obesity, COPD and thyrotoxicosis) independent of the dose of drug received. [241] However, few demonstrate that in patients with cardiac risk factors (with the exception of hypertension) there is an increased association between the development of CHF and treatment. In a SEER investigation of NHL patients who received anthracyclines, hypertension is the only cardiac risk factor that showed an association with heart failure. [242]

In a retrospective study utilizing the SEER database, Doyle and colleagues evaluated chemotherapy use and cardiotoxicity among elderly women in the general population diagnosed with early-stage breast cancer. The authors hypothesized those elderly breast cancer patients who received chemotherapy, especially doxorubicin-based regimens, would experience higher rates of cardiotoxicity than patients who did not receive chemotherapy. Data were collected for each patient beginning 12 months prior to diagnosis, continuing to death censoring on December 31, 2001. [243]

The following outcomes were measured: cardiomyopathy, CHF, heart disease (HD) and myocardial infarction. Heart disease (HD) was a composite that included diagnosis codes for cardiomyopathy, acute myocarditis, CHF, acute MI, arrhythmias,

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[241] Marianne Ryberg et al., "New Insight Into Epirubicin Cardiac Toxicity: Competing Risks Analysis of 1097 Breast Cancer Patients," *J. Natl. Cancer Inst.* 100, no. 15 (2008): 1058–1067.

[242] Dawn L Hershman and Theresa Shao, "Anthracycline Cardiotoxicity After Breast Cancer Treatment.," *Oncology* 23, no. 3 (March 2009): 227–234; Hershman et al., "Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma."

[243] John Doyle et al., "Chemotherapy and Cardiotoxicity in Older Breast Cancer Patients: A Population-Based Study," *Journal of Clinical Oncology* 23, no. 34 (December 1, 2005): 8587–8605.

ventricular dysfunction, ischemic heart disease and sudden death. The authors concluded that even when accounting for any baseline heart disease, patients who receive the anthracycline-based regimen had a higher risk of cardiomyopathy. [244]

2.4.2.1   Combination Therapy

Certain combination therapies such as treatment with radiation, trastuzumab or taxanes may increase the risk of heart failure.[245] In a meta-analysis by the Early Breast Cancer Trialists' Group, the investigators found an increase in vascular mortality associated with radiation therapy, and this risk increased with advancing age. [246] Smaller studies have suggested that left-sided radiation with higher cumulative doses of anthracyclines may exacerbate the drugs cardiac toxicity, although recent studies have not found that association when standard dose doxorubicin is given for four or fewer cycles. [247]

Amplification and over-expression of HER-2 is seen in 20 – 30% of breast cancer patients and leads to less favorable outcomes. [248]Trastuzumab is a monoclonal antibody that targets the extracellular domain of HER-2 and improves the outcome in patients who have over-expression of this receptor.[249] During the drug approval trials for trastuzumab,

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[244] Ibid.

[245] Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy."

[246] M Clarke et al., "Effects of Radiotherapy and of Differences in the Extent of Surgery for Early Breast Cancer on Local Recurrence and 15-year Survival: An Overview of the Randomised Trials," *Lancet* 366, no. 9503 (December 17, 2005): 2087–2106.

[247] Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy."

[248] Leyland-Jones, "Trastuzumab: Hopes and Realities."

[249] E. Tan-Chiu, "Assessment of Cardiac Dysfunction in a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel, With or Without Trastuzumab As Adjuvant Therapy in Node-Positive, Human Epidermal Growth Factor Receptor 2-Overexpressing Breast Cancer: NSABP B-31," *Journal of Clinical Oncology* 23, no. 31 (2005): 7811–7819.

there was a significant increase in heart failure (either symptomatic or asymptomatic) in patients who received trastuzumab with anthracyclines when compared to trastuzumab alone or paclitaxel. Later trials avoid the concomitant use of the two as it is believed that trastuzumab somehow potentiates the cardiotoxicity of the anthracycline. [250]

The Cardiac Evaluation and Review Committee (CREC), which is part of FDA, reviewed all trials in which trastuzumab was being evaluated, to determine criteria for diagnosis of a cardiac dysfunction. The established criteria used to evaluate trastuzumab cardiotoxicity includes: cardiomyopathy characterized by global decrease in LVEF, signs or symptoms of heart failure, decline of LVEF of at least 5% to less than 55% with signs and/or symptoms of heart failure, or decline of LVEF of at least 10% to less than 55% without signs and/or symptoms of CHF. [251]

A prospective study by Tan-Chiu and colleagues was designed to determine the increase in cardiac dysfunction when trastuzumab is added to a standard regimen of AC plus paclitaxel. Episodes of cardiac dysfunction were classified using the NYHA classification system and only NYHA class III or IV were considered to be CHF. Both arms received AC plus paclitaxel and the study arm received trastuzumab. Cardiac monitoring included a cardiac history form submitted at enrollment, every six months for five years and then annually thereafter. MUGA scans were done at study entry, after AC, and at six, nine and 18 months. Additional scans were allowed at the discretion of the investigator. [252]

[250] Kenneth R Chien, "Herceptin and the Heart -- A Molecular Modifier of Cardiac Failure," *N Engl J Med* 354, no. 8 (2006): 789–790.

[251] James Speyer, "Cardiac Dysfunction in the Trastuzumab Clinical Experience," *J Clin Oncol* 20, no. 5 (2002): 1156–1157.

[252] Tan-Chiu, "Assessment of Cardiac Dysfunction in a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel, With or Without Trastuzumab As Adjuvant Therapy in Node-Positive, Human Epidermal Growth Factor Receptor 2-Overexpressing Breast Cancer: NSABP B-31."

Trastuzumab was started in the study arm patients if their LVEF did not drop more than 15 % below the pre-entry level or was still above the lower limit of normal (LLN). The study protocol included explicitly stated criteria on whether to continue or suspend use of trastuzumab. Criteria used by the review panel were similar to the CERC, and included NYHA class III or IV symptoms with a decrease of LVEF of > 10% to lower than 55%, or a decrease of 5% to less than the lower limit of normal (LLN). Patients with reported cardiac dysfunction continued to be monitored via MUGA scans. [253]

The primary end point was the difference in cardiac dysfunction between study arms (reported cardiac dysfunction or death). These authors concluded that the reduction in recurrence and mortality that trastuzumab gave patients was an acceptable risk in patients with HER-2 positive, node positive disease. However, in older patients with cardiac risks or who have LVEF decline after administration of AC to the LLN, the risk may be too great. [254]

Taxanes also are believed to potentiate the cardiotoxicity of anthracyclines by possibly stimulating the conversion of doxorubicin to its more cardiotoxic metabolite in the myocardial tissue. However, an increase in heart failure incidence is only seen at higher cumulative doses of doxorubicin and in combination therapy, but not when taxanes are given in the adjuvant setting. [255]

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[253] Ibid.

[254] Ibid.

[255] Hershman and Shao, "Anthracycline Cardiotoxicity After Breast Cancer Treatment."

2.4.2.2   Dose-Dependence

There is a consensus that the incidence of chemotherapy-induced cardiotoxicity is dose-dependent. [256] Published results report a wide range regarding anthracycline-induced heart failure incidence. This can be attributed to differences in how the authors defined "low", "medium" or "moderate", or "high" doses, as well as how heart failure was defined (whether studies reported only symptomatic dysfunction). Values reported in literature can range from, for example, > 4, > 18 or $> 36\%$ in patients receiving cumulative doses of 500-550 mg/m^2, 551-600 mg/m^2 or > 600 mg/m^2 respectively, while other reviews report cardiotoxic incidence of 0.14%, 7% and 18% at doses of $<$ 400mg/m^2, 550 mg/m^2 and 700mg/m^2 respectively. A study in 1979 by Von Hoff and colleagues reported incidences of 3%, 7% and 18% for doses of 400 mg/m^2, 550 mg/m^2 and 700 mg/m^2 respectively[257]. In a more recent study by Swain and colleagues, the authors suspected that previous reports were underestimated. They found incidences of 5%, 26% and 48% with the same respective doses. [258] See Figure 2.3 for a comparison of these findings.

In another retrospective study by Lefrak and colleagues which included 399 patients, the results showed a clear association between dose and incidence of cardiotoxicity. The authors concluded that incidence rose to unacceptably high levels when the cumulative doses exceeded 500 mg/m^2. The incidence values reported were > 4, > 18 or $\sim 36\%$ of patients who had received cumulative doses of 500 - 550 mg/m^2, 551 -

[256] Sandra M. Swain, Fredrick S. Whaley, and Michael S. Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin," *Cancer* 97, no. 11 (2003): 2869–2879.

[257] Von Hoff et al., "Risk Factors for Doxorubicin-Induced Congestive Heart Failure."

[258] Swain, Whaley, and Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin."

600 mg/m^2 or > 600 mg/m^2 respectively. [259] In a review by Shan et al. the authors give a dose dependent relationship as follows: at doses < 400 mg/m^2 the incidence of chronic cardiotoxicity is 0.14%, this incidence rises to 7% at a dose of 550 mg/m^2, and to 18% at a dose of 700mg/m^2. [260]

Figure 2.3 Comparisons of Reported Incidences of Dose-Dependent, Anthracycline-Induced Heart Failure [261]

Estimation of doxorubicin-induced CHF

	400 mg/m²	550 mg/m²	700 mg/m²
Von Hoff	3%	7%	18%
Swain	5%	26%	48%
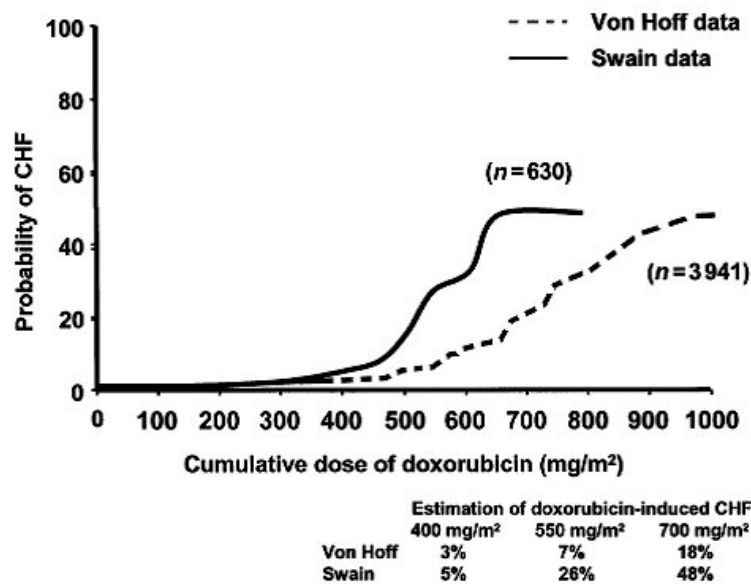
[259] E A Lefrak et al., "A Clinicopathologic Analysis of Adriamycin Cardiotoxicity," *Cancer* 32, no. 2 (1973): 302–314.

[260] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[261] Swain, Whaley, and Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin."

In a prospective study to assess the cardiac effects of two different cumulative doses of adjuvant doxorubicin and radiation therapy in breast cancer patients, Shapiro and colleagues randomized patients to receive AC (n = 299) for either 5 or 10 cycles, 122 of these patients also received radiation. Cardiac events were compared to the Framingham Heart Study (which served as the control). The planned cumulative doses of doxorubicin were 225 or 450 mg/m^2. [262] Patients with CHF, history of MI or cardiomyopathy were ineligible. After completion of chemotherapy, there was a second randomization to receive RT or observation. Patients who did not participate in the secondary randomization also received adjuvant chest wall and regional nodal RT after the completion of chemotherapy. [263]

Medical records were reviewed for the development of cardiac events from the time of initial randomization until the most recent follow up or death. Cardiac events were defined as either symptomatic CHF or MI. Follow up was available in 92% of randomized patients.[264] Verification of CHF was based on physical exam findings, use of heart failure treatment, or diminished LVEF. All records initially identified as having a cardiac event and a randomly selected group of 68 patients were reviewed by a cardiologist (blinded). Identification of cardiac events were concordant in 21/23 cases, two cases were excluded by cardiologists because of insufficient evidence. After the blinded review, another patient with a cardiac event was identified, bringing the total to 22. [265]

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[262] Shapiro et al., "Cardiac Effects of Adjuvant Doxorubicin and Radiation Therapy in Breast Cancer Patients."
[263] Ibid.
[264] Ibid.
[265] Ibid.

For purposes of analysis, the cardiac RT dose volume for primary breast cancer was retrospectively categorized as low (defined as the treatment of right sided breast cancers with tangential fields), moderate (as the treatment of left sided breast cancers with tangential fields) or high (treatment of right or left breast cancers with tangential fields and of a separate anterior field for the internal mammary nodes). [266]Cardiac events were analyzed in two ways. The first method included cardiac events censored for recurrence (i.e., only cardiac events that preceded a documented breast cancer recurrence or a diagnosis of contralateral breast cancer). The second method included cardiac events uncensored for recurrence and consisted of all cardiac events irrespective of their timing in relation to breast cancer recurrence or contralateral breast cancer. Results of two methods did not differ substantially. Cardiac events occurred in 22 of 276 patients, CHF in 19 and AMI in 5, two patients had CHF and AMI during the same hospitalization, no patient with a cardiac event had a prior history of cardiac disease except hypertension. Observed cardiac events in the five-cycle group were not higher than the general population (when comparing to the population in the Framingham Heart Study) regardless which radiotherapy dose was given. In the ten-cycle group, patients had a 3.4 fold higher risk of cardiac events than the patients in the five-cycle group and a 3.6 fold higher risk than the general population.[267]

A prospective study, by Ryberg and colleagues, was designed to evaluate cumulative dose, dose intensity, single dose level and schedule of epirubicin on the development of CHF in breast cancer patients. The sample included 469 patients, and only patients that were in NYHA class II-IV were classified as having heart failure. Patients could not have had prior anthracycline therapy before epirubicin therapy and

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[266] Ibid.

[267] Ibid.

patients with evidence of cardiac dysfunction (CHF, MI or arrhythmia) were excluded. The primary end point of this trial was clinical CHF as defined by reported history of breathlessness, clinical signs of CHF (dyspnea/congestion on x-ray, peripheral edema), an X-ray showing cardiomegaly with or without pulmonary congestion or pleural effusion, an abnormal LVEF (LVEF < 46% absolute value or a decrease of >15% from baseline) and, if possible, an abnormal echo. [268]

2.4.3 PREVENTIVE STRATEGIES

There are a number of strategies that have been used in an attempt to decrease the incidence of treatment-related heart failure. Such strategies include increasing the infusion time, changing administration schedule, limiting the cumulative dose to $\leq$ 300 mg/m^2, using anthracycline analogs (e.g., epirubicin, idarubicin and mitoxantrone), liposomal or pegylated-liposomal formulations and protective agents. Other strategies such as dietary supplements and nutrients have demonstrated some benefit in animal models but have not translated to productive use in humans. [269] Table 2.4 lists the potential strategies to prevent treatment-related heart failure, how each strategy is classified and the proposed mechanism for cardioprotection.

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[268] M. Ryberg et al., "Epirubicin Cardiotoxicity: An Analysis of 469 Patients with Metastatic Breast Cancer," *Journal of Clinical Oncology* 16, no. 11 (1998): 3502.

[269] Karlijn A. Wouters et al., "Protecting Against Anthracycline-induced Myocardial Damage: a Review of the Most Promising Strategies," *British Journal of Haematology* 131, no. 5 (2005): 561–578.

Table 2.4 Proposed Anthracycline Cardiotoxicity Prevention Strategies [270]

Agent	Class	Mechanism
Dexrazoxane	Chelating Agent	Binds to Iron; Prevents Free Radical Formation; Inhibits DNA Topoisomerase
NAC	Mucolytic	Promotes Endogenous Antioxidant Synthesis
Carnitine	Dietary Supplement	Antioxidant; Transfer of Long-Chain Fatty Acids into Mitochondria
Probucol	Lipid-Lowering Drug	Promotes Endogenous Antioxidant Synthesis
Amifostine	Cytoprotective Agent	Scavenges Free Radicals
Carvedilol	Beta-Adrenergic Antagonist	Prevents Free Radical Formation; Prevents Depletion of Endogenous Antioxidants
Vitamins A,E, and C; Carotenoids	Nutrient	Antioxidant
Selenium	Trace Element	Antioxidant; Anti-Carcinogenic Action
Glutathione	Tri-Peptide Thiol	Antioxidant
Coenzyme Q10	Dietary Supplement	Antioxidant

NAC: N-Acetylcysteine

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[270] Ibid.

There are conflicting opinions as to whether increasing the infusion time is beneficial, some think that giving a slower infusion over longer periods decreases the peak anthracycline level, however, it also prolongs the exposure of myocytes to the drug. There is evidence that the longer infusion times prevents the immediate cardiotoxic effects, however, no differences have been noted in late cardiac manifestations. [271] While there is evidence that schedules with extended infusions have fewer cardiotoxic events than bolus dosing, there are disadvantages to this dosing strategy. The extended infusions usually require the placement of a central line which can increase costs either directly if a hospital stay is required or indirectly through increased complications such as infection or thromboembolism. [272] The weekly administration schedule has also been shown to slightly decrease the incidence of cardiotoxic events[273]; however, this brings patients back to the clinic every week, increasing inconvenience to both them and the physician, and could potentially overlap other drugs in the regimen which could increase side effects (e.g. myelosuppression). [274]

2.4.3.1   Pegylated/Liposomal Anthracycline Formulations

The purpose of the liposomal formulations is to maintain the anti-tumor effect of the drug while reducing toxicity, there are several proposed ways that this is made possible. Human vasculature has walls that are made of endothelial cells and between those cells are tight junctions. The tight junction prevents leakage of larger particles into

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[271] Ibid.

[272] M Bates, "A Pharmacoeconomic Evaluation of the Use of Dexrazoxane in Preventing Anthracycline-Induced Cardiotoxicity in Patients with Stage IIIB or IV Metastatic Breast Cancer," *Clinical Therapeutics* 19, no. 1 (1997): 167–184.

[273] Von Hoff et al., "Risk Factors for Doxorubicin-lnduced Congestive Heart Failure."

[274] Bates, "A Pharmacoeconomic Evaluation of the Use of Dexrazoxane in Preventing Anthracycline-Induced Cardiotoxicity in Patients with Stage IIIB or IV Metastatic Breast Cancer."

the extravascular space keeping them in circulation. This anatomical phenomenon theoretically can achieve both goals. Liposomes have larger structures than the regular drug making it impossible for the escape through the capillary junctions in the heart and GI tract, thereby keeping them in the vascular space increasing delivery to the tumor itself. Tumor cells lack tight junctions; therefore drugs that are encapsulated in liposomes get higher concentrations to the intended site of action (and conversely lower concentrations where problematic adverse events occur such as cardiac tissue). [275]

The decreased leakage into the extravascular space can hypothetically grant the ability to administer the encapsulated drug at much higher doses than the conventional formulation because of the proposed lower toxicity potential. Two additional advantages of these drug formulations include, 1) formulating the drug within liposomes slows release, keeping peak levels lower, which should decrease toxicity, [276] and 2) the addition of pegylated (polyethylene glycol) encapsulation gives the drug a much longer half-life than liposomal formulations (> 55 hours compared to two to four hours) which is attributed to the decreased degradation and uptake by the mononuclear phagocyte system. [277]

In a prospective, multi-center trial, 224 patients were randomized to receive liposomal doxorubicin (n = 108) or conventional doxorubicin (n = 116) in the first-line treatment of metastatic breast cancer. The primary efficacy end point was response rate (RR) and a primary safety end point of cardiotoxicity. Patients were excluded if their only site of metastasis was bone; prior chemotherapy was received in the six months prior to randomization, patients with brain metastasis, radiation to more than 50% of the bone

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[275] Jones, Swanton, and Ewer, "Anthracycline Cardiotoxicity."

[276] Wouters et al., "Protecting Against Anthracycline-induced Myocardial Damage: a Review of the Most Promising Strategies."

[277] Jones, Swanton, and Ewer, "Anthracycline Cardiotoxicity."

marrow or mediastinal radiation greater than 3500 cGy, women who were pregnant or lactating, or patients with congestive heart failure, arrhythmia or myocardial infarction in the six months prior to enrollment. [278]

In the analysis for efficacy, the time to progression (TTP) and time to treatment failure (TTF) were similar among the treatment groups. There was a slight trend toward increased survival in the conventional doxorubicin group, however, this was not statistically significant ($p = 0.09$). Cardiac events of severity sufficient for removal from the study were 29% versus 13% in the conventional and liposomal groups respectively ($p = 0.0001$). Congestive heart failure developed in two patients (2%) in the liposomal doxorubicin group compared to nine patients (8%) in the conventional doxorubicin group, three of which developed CHF within 30 days of their last dose. These authors concluded that their findings of reduced cardiotoxicity support the use of the liposomal formulation. [279]

A phase II study designed to examine the response rate and toxicity of liposomal doxorubicin found conflicting results. The study enrolled 52 patients that had not received prior treatment for metastatic disease. Response was categorized as one of the following: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Almost half of the patients had received chemotherapy in the adjuvant setting (42%), 12 of these received anthracyclines. [280]

[278] Lyndsay Harris et al., "Liposome-encapsulated Doxorubicin Compared with Conventional Doxorubicin in a Randomized Multicenter Trial as First-line Therapy of Metastatic Breast Carcinoma," *Cancer* 94, no. 1 (2002): 25–36.

[279] Ibid.

[280] C. L Shapiro et al., "Phase II Trial of High-Dose Liposome-Encapsulated Doxorubicin With Granulocyte Colony-Stimulating Factor in Metastatic Breast Cancer," *J Clin Oncol* 17, no. 5 (1999): 1435–.

Twenty patients (38%) experienced cardiotoxicity, (grade three toxicity [n = 4], grade four toxicity [n = 3]). The only risk factors that were significant in the authors logistic regression model were the prior cumulative doxorubicin dose (p = 0.007) and the cumulative dose of liposomal doxorubicin (p = 0.032). The overall response rate observed in this study was 46% (CR in three patients [6%], PR in 20 [40%]). The authors compared this finding to that of four trials of single agent conventional doxorubicin that yielded response rates between 27% and 36% and concluded that their results were only marginally better and hardly justified the increased toxicity. [281]

2.4.3.2   Anthracycline Analogs

While doxorubicin is the most common anthracycline used is breast cancer regimens, there is evidence that supports the substitution of epirubicin into similar chemotherapy regimens (i.e., using epirubicin instead of doxorubicin with 5FU and cyclophosphamide FEC instead of FAC). However, these substitutions are not without cardiac risk, in fact, dose-dependent cardiotoxicity is also observed when other anthracycline agents are used. For trials that report a lower incidence of cardiotoxicity when epirubicin is substituted for doxorubicin, the protocols are often using mg per mg substitution. The NCCN guidelines for the treatment of breast cancer recommend protocols where doxorubicin is typically dosed at 50 or 60 mg/m^2, the corresponding dose of epirubicin to be used is 90 or 100 mg/m^2. Therefore, the dose used in the trial needs to

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[281] Ibid.

be considered when evaluating the cardiotoxicity of epirubicin or other anthracycline analog. [282]

In a prospective study by Gennari and colleagues designed to determine the role of cardiac risk factors in cardiotoxicity, the investigators enrolled 105 patients who were to receive epirubicin/paclitaxel treatment either with (n = 76) or without (n = 29) gemcitabine. Patients with a prior history of cardiac disease or signs of cardiac dysfunction were excluded, however, prior adjuvant therapy was allowed if completed more than six months before enrollment. The use of prior hormone therapy was allowed, and prior anthracycline therapy was allowed if the total cumulative dose was < 180 mg/m^2 for doxorubicin and < 360 mg/m^2 for epirubicin. [283]

Pre-existing cardiac risk factors that were considered included: hypertension, diabetes, and chest wall irradiation on either the right or left. The primary endpoint of the study was cardiac failure defined by NYHA classification. There were nine patients that experienced CHF during follow up, five of which received cumulative epirubicin doses between 450 and 720 mg/m^2, and the remaining four patients received the maximum dose allowed per protocol of 1,080 mg/m^2. While there was no clear relationship demonstrated between the risk factors and heart failure, seven of nine patients who developed heart failure received chest wall irradiation. [284]

The authors calculated cumulative probabilities of developing heart failure and concluded that those patients with one risk factor a had similar probability to those without any risk factors up to cumulative dose of 990 mg/m^2 (cumulative risk 10% and 12% respectively). After adjustment for cumulative dose, there was no difference in the

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[282] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

[283] A. Gennari et al., "Cardiotoxicity of Epirubicin/paclitaxel-containing Regimens: Role of Cardiac Risk Factors," *Journal of Clinical Oncology* 17, no. 11 (1999): 3596.
[284] Ibid.

incidence in CHF between those with risk factors and those patients without. Of note, none of the patients who received gemcitabine developed heart failure. Of those patients who had consolidation and subsequent BMT, only one developed heart failure.[285]

The authors concluded that the substitution of epirubicin for doxorubicin had a lower incidence of heart failure, and that the substitution is acceptable up to doses of 990 mg/m^2. These authors suggest that this may be more clinically evident in patients who have received prior chest wall irradiation; however the small number of observations in the study makes definitive conclusions impossible. The authors also suggest that if patients have a risk factor or have had epirubicin adjuvant therapy in the past, a reduction from eight cycles to six may be possible. [286]

In another prospective study by Nielson and colleagues that was specifically designed to assess the cardiac toxicity of epirubicin in patients with advanced breast cancer, heart failure was assessed with advanced LVEF methods. Inclusion criteria for the study were patients admitted with metastatic or unresectable progressive breast cancer, age < 70, WHO performance status ≤ 3, no concomitant cancers, no brain or leptomeningeal involvement, no previous treatment with anthracyclines or vinca alkaloids, and no clinical evidence of cardiac disease defined as CHF, MI or arrhythmia.[287]

Pretreatment evaluation of cardiac function included physical exam, chest x-ray, ECG and LVEF. The exam was repeated prior to each dose, the ECG was repeated every 1 to 3 months and LVEF was obtained at cumulative doses of 300, 600 and 900 mg/m^2 and each subsequent 100 mg/m^2 thereafter. Cardiac toxicity was defined as LVEF ≤ 45%

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[285] Ibid.

[286] Ibid.

[287] D Nielsen et al., "Epirubicin Cardiotoxicity: a Study of 135 Patients with Advanced Breast Cancer," *J Clin Oncol* 8, no. 11 (November 1, 1990): 1806–1810.

or a decrease of $\geq 15\%$ from pretreatment level; only patients in NYHA classes II - IV were considered having heart failure. Of the 11 patients who received doses > 1000 mg/m^2, seven developed CHF and four subsequently died. There were six patients who received doses between 500 and 1000 mg/m^2, of those, one patient developed CHF. Overall, this study reported a 6% total incidence of CHF. These authors concluded that epirubicin in cumulative doses > 1000 mg/m^2 increased cardiac risk and death from heart failure, and doses between 500 - 1000 mg/m^2 increased risk of heart failure. They also concluded that LVEF is not a valuable predictor of heart failure and should only be measured as part of the work-up. [288]

Prior to the beginning of this trial there was not an established maximum dose of epirubicin, there were four patients who had fatal cases of CHF who received doses of 1,081, 1,094, 1,211, and 1,317 mg/m^2. [289] Following this trial the maximum recommended dose was reduced to 1000 mg/m^2. [290] The authors used Kaplan-Meier estimates and logistic regression to determine risk where an event was defined as the development of CHF. There were 34 patients (7.2%) that developed CHF. Results showed an association of heart failure to the cumulative dose received, patients who received higher cumulative doses were more likely to develop heart failure (p = 0.001). The authors also listed schedule, mean dose intensity, mean single dose level and prior radiation therapy as possible risk factors but did not find a significant difference in heart failure incidence. Additionally, previous treatment with CMF was not found to be a risk factor. These authors concluded that epirubicin was cardiotoxic, and that the maximum

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[288] Ibid.

[289] Ibid.

[290] Ryberg et al., "Epirubicin Cardiotoxicity."

dose should be 900 mg/m^2. They also stated that radiation against the heart leads to an increased risk of developing heart failure and an accelerated death. [291]

2.4.3.3   Protective Agents

Dexrazoxane (DZR) is a protective agent that is a derivative of EDTA; it can reduce the amount of free iron in the myocytes by producing its own free radicals that decrease the oxidized iron levels during the anthracycline infusion. DZR is usually reserved for patients with metastatic disease who have received over 300 mg/m^2 of doxorubicin. It is typically not recommended at the beginning of therapy because there is a possibility it may decrease the anti-tumor effect of the doxorubicin. Dose-limiting strategies have reduced the reported incidence of heart failure (i.e., doses in the range of 240 - 360) to 1.6%; however incidence increases to 2.1% in those patients receiving subsequent paclitaxel and the newer targeted drugs such as trastuzumab. While dose-limiting strategies have decreased heart failure incidence, they also appear to negatively affect outcomes such as survival and cure. [292]

A retrospective analysis of three studies sought to determine whether heart failure was under-reported. To determine this, they analyzed data from the placebo arms of three trials, which included two breast cancer trials and one lung cancer trial. The studies included were placebo controlled trials to examine the protective effect of dexrazoxane (DZR) on development of heart failure. The primary objective of the analysis was to

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[291] Ibid.

[292] L. Gianni et al., "Paclitaxel by 3-hour Infusion in Combination with Bolus Doxorubicin in Women with Untreated Metastatic Breast Cancer: High Antitumor Efficacy and Cardiac Effects in a Dose-finding and Sequence-finding Study," *Journal of Clinical Oncology* 13, no. 11 (1995): 2688; Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

examine the relationship between the cumulative doxorubicin dose and the cumulative probability of developing doxorubicin related CHF. [293]

The three studies were all randomized, double-blind, multicenter studies evaluating cardiotoxicity in patients receiving dexrazoxane in combination with a doxorubicin containing regimen. None of the trials established a maximum dose for doxorubicin and none of the patients had prior anthracycline therapy. The two breast studies had identical protocols, and the lung protocol was similar to the protocols of the other two studies. All three studies showed clear evidence of significant cardioprotection of dexrazoxane, so all patients randomized to receive placebo were switched to receive DZR with the seventh cycle of treatment. All patients randomized to received placebo were included in the analysis (N = 630). Of these, 168 were switched to open label DZR. [294]

The incidence of doxorubicin-induced heart failure in the study was compared to a previous retrospective analysis by Von Hoff et al. These authors observed estimated cumulative percentage of 5% of patients at 400 mg/m^2, increasing to 26% at 550 mg/m^2, 48% at 700 mg/m^2 compared to 3%, 7% and 18% reported in the Von Hoff et al. review. The authors concluded that doxorubicin-related heart failure occurs more often than previously thought. Additionally, they concluded that LVEF is not a sensitive test for predicting CHF, and laboratory tests, such as cardiac troponins might be better able to detect heart failure than using LVEF. [295]

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[293] Swain, Whaley, and Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin."
[294] Ibid.
[295] Ibid.

2.4.4 MANAGEMENT OF CARDIOTOXICITY

Treatment options for drug-induced heart damage are similar to that of other etiologies, consisting of medical management and surgical therapy. Anthracycline-induced heart failure, whether the patients are experiencing symptoms or not, is related to high mortality rates and low quality of life. The one- and two-year mortality for patients in NYHA classes III or IV is 40% and 60% respectively. Adults without symptoms (i.e., NYHA classes I or II) have a 50% mortality rate within 7 years. [296] This illustrates the importance of early detection and prevention of further deterioration of cardiac function.

Heart failure treatment typically includes medications such as ACE inhibitors, beta-blockers, diuretics and aldosterone inhibitors; however, these patients do not typically see the same response from medication as heart failure patients with typical etiologies. [297] Therapy in later stage patients may require more invasive interventions; these can be experimental procedures such as cardiomyoplasty, ventriculectomy and cell transplantation, or procedures that are common in clinical practice like transplantation or insertion of ventricular assist devices (including artificial hearts). A proposed graphic for management is illustrated in Figure 2.4. [298]

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[296] Wouters et al., "Protecting Against Anthracycline-induced Myocardial Damage: a Review of the Most Promising Strategies."

[297] Stefan Christiansen and Rudiger Autschbach, "Doxorubicin in Experimental and Clinical Heart Failure," *European Journal of Cardio-Thoracic Surgery* 30, no. 4 (October 2006): 611–616.

[298] Ibid.

Figure 2.4 Proposed Strategies for Management of Patients with Doxorubicin-Induced Cardiac Dysfunction [299]
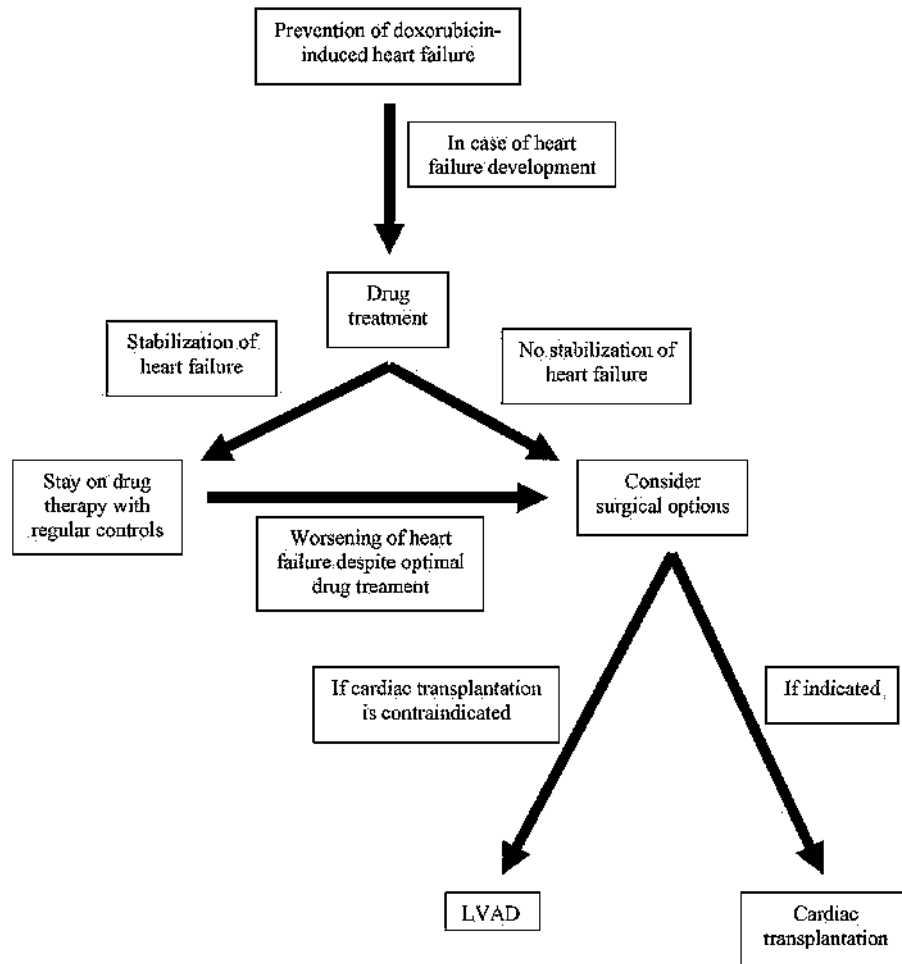
2.4.4.1   Medications

As previously discussed, there are a number of medications that have been shown to improve morbidity and mortality in heart failure; however, guidelines do not yet exist for patients specifically with chemotherapy-induced heart failure. Patients with this type of heart failure have not been shown to experience the same improvement from medication therapy.

An early observation by Lefrak and colleagues noted that this type of cardiomyopathy does not respond as well to typical medication therapy. [300] Although, that observation was made in 1973, most experts continue to agree. [301] Contrary to those findings, in a retrospective review by Haq and colleagues designed to look at mortality, these authors concluded that patients did respond well to medication therapy (which included digoxin and diuretics at the time of publication). [302]

Most of the prospective trials examining effects of medication on chemotherapy-induced heart failure have been conducted in survivors of childhood cancers and have extremely small sample sizes. A small observational study (n = 3) which included pediatric patients, found that the addition of metoprolol to standard medications (i.e., digoxin, furosemide, captopril) improved symptoms within two months. Additionally, these investigators found that indices such as ejection fraction also improved over the follow-up period which was five to 30 months. However, long-term outcomes were not available. [303]

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[300] Lefrak et al., "A Clinicopathologic Analysis of Adriamycin Cardiotoxicity."
[301] Singal and Iliskovic, "Doxorubicin-Induced Cardiomyopathy."
[302] Haq et al., "Doxorubicin-induced Congestive Heart Failure in Adults."
[303] Robert E. Shaddy et al., "Efficacy and Safety of Metoprolol in the Treatment of Doxorubicin-induced Cardiomyopathy in Pediatric Patients," *American Heart Journal* 129, no. 1 (January 1995): 197–199.

In a randomized, double-blind, placebo-controlled trial, 135 survivors of childhood cancer were identified that had at least one cardiac abnormality after exposure to anthracyclines. The study was designed to test an intervention to prevent or slow progression. The outcomes in this study included maximal cardiac index (MCI), left ventricular end-systolic wall stress (LVESWS), shortening fraction (SF), and stress-velocity index (SVI). There was an initial drop in LVESWS in the first year of treatment and this improvement was maintained throughout the follow-up period, however, it was not statistically significant when compared to the placebo group. The other outcome indices also did not yield statistically significant improvements, even after the prediction model was corrected for anthracycline dose received, female gender, treatment with radiation, if age of cancer diagnosis was ≤ 3, and years since treatment with anthracycline ≥ 10. The study had a three-year follow-up period and the authors concluded that the short follow-up may be the reason for the lack of statistically-significant improvement in the treatment group.[304]

In a retrospective study examining the potential long-term benefit of enalapril, the investigators reviewed the charts of 18 survivors of childhood cancer. For inclusion into the study, patients were exposed to anthracyclines, had received enalapril, and had records of ECHO's during therapy. Outcome criteria included both systolic and diastolic blood pressure and ECHO measurements (LV end-diastolic dimension, LV end-diastolic posterior wall thickness, LV afterload [end-systolic wall stress], LV contractility [stress-velocity index], LV fractional shortening, and LV mass). [305]

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[304] Jeffrey H Silber et al., "Enalapril to Prevent Cardiac Function Decline in Long-Term Survivors of Pediatric Cancer Exposed to Anthracyclines," *J Clin Oncol* 22, no. 5 (2004): 820–828.

[305] Steven E Lipshultz et al., "Long-Term Enalapril Therapy for Left Ventricular Dysfunction in Doxorubicin-Treated Survivors of Childhood Cancer," *J Clin Oncol* 20, no. 23 (2002): 4517–4522.

These investigators found that there appeared to be improvement in the first several years of follow-up, but any beneficial effect was temporary. Patients initially with asymptomatic disease (n = 12) trended back to baseline after six to ten years of drug therapy; for symptomatic patients (n = 6), improvements lasted two to six years. These authors did find that those patients with CHF when starting on medication were more likely to show initial improvements. After six years of follow-up, nine patients either died or were referred for transplant; this included all six patients that began the study period with symptomatic disease and three patients who were initially asymptomatic. The authors concluded that enalapril did not appear to prevent progression of advanced disease, and select patients may benefit from enalapril therapy such as intermediate follow-up of asymptomatic patients or short-term treatment in patients with dilated cardiomyopathy. [306]

To determine the effect of traditional medication therapy on doxorubicin-induced heart failure, a prospective study was conducted by Tallaj and colleagues. Investigators enrolled 25 patients that were referred to their center from 1990 to 2003 with a diagnosis of doxorubicin-induced cardiomyopathy. Patients were grouped based on therapy received (ACE inhibitors (n = 23) or ARB (n = 2) ± Beta Blockers (n = 15)), with the majority (88%) in NYHA classes III or IV. With drug therapy, both LVEF (p = 0.022) and NYHA class (p < 0.003) improved over the follow-up period. When comparing the different treatment groups, the combination therapy group had a significantly greater improvement in LVEF than the mono-therapy group (p = 0.028). Four patients died, three

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[306] Ibid.

were in the combination therapy group and two deaths were attributed to progressing heart failure. [307]

These authors concluded that the outcomes may not be as grim as previously thought, based on their study's results showing a ten-year survival greater than 60%. However, the total cumulative dose of doxorubicin was only known in ten patients and potential use of combination therapy was not known for any of the study participants. The authors conceded that their small sample was a limitation and recognized that more studies would have to be conducted, but that their results did show that medication therapy could be useful. [308]

2.4.4.2   Surgical Options

Transplant was once considered the only therapeutic option for cardiac functional improvement in heart failure patients. There is a common limitation- the shortage of organs (a barrier for all heart failure patients). The use of transplantation in cancer patients elicits unique challenges. Typically, the most frequently encountered barrier to transplantation is the requirement that patients have evidence of cure or remission of the disease for at least five years. [309] An additional barrier unique to cancer patients is that anti-rejection agents have the potential to increase the possibility of recurrence or development of second malignancies. Therefore, because of the challenges to receiving

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[307] Jose A. Tallaj et al., "Response of Doxorubicin-induced Cardiomyopathy to the Current Management Strategy of Heart Failure," *The Journal of Heart and Lung Transplantation* 24, no. 12 (December 2005): 2196–2201.

[308] Ibid.

[309] Mandeep R. Mehra et al., "Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates--2006," *The Journal of Heart and Lung Transplantation* 25, no. 9 (2006): 1024–1042.

this intervention, in patients with or without cancer, other therapeutic modalities in late- or end-stage disease are needed. [310]

As a result of the continually evolving criteria for selection for organ transplantation, transplants have been successfully performed in cancer survivors. A retrospective study was conducted to determine outcomes in cancer patients who subsequently developed cardiomyopathy in a single transplant center. That facility had performed heart transplants in nine patients who developed cardiomyopathy post chemotherapy during the data collection period. Three patients died during the follow-up period, causes of death were sepsis, graft failure and recurrence of malignancy. The six remaining patients achieved survival similar to patients who had undergone transplant without a prior history of malignancy. [311] However, since the mean age of these patients was about 30 years old and the sample was extremely small, it may be unrealistic to expect similar outcomes in a larger study from multiple centers.

There are other surgical procedures that could be used, including ventricular assist devices (VASD) and ventricular restoration procedures. Either could be used as a bridge to transplant or as destination therapy. The goals of ventricular restoration surgery are typically to reduce the chamber volume and attempt to restore the shape/geometry of the ventricle. The technique shows increases of LVEF of 29.6% to 39.5% and a corresponding decrease in left ventricular end diastolic volume. Additionally, the five-year survival of patients after this procedure is almost 70%. [312]

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[310] J. K. Patel and J. A. Kobashigawa, "Heart Transplantation," *Circulation* 124, no. 4 (July 2011): e132–e134.

[311] A M Grande et al., "Heart Transplantation in Chemotherapeutic Dilated Cardiomyopathy.," *Transplantation Proceedings* 35, no. 4 (June 2003): 1516–1518.

[312] Francesco Nicolini and Tiziano Gherli, "Alternatives to Transplantation in the Surgical Therapy for Heart Failure," *European Journal of Cardio-Thoracic Surgery* 35, no. 2 (February 2009): 214–228.

The use of ventricular assist devices and heart transplantation are common procedures for patients with late- or end-stage disease. Ventricular assist devices are typically used for one of three reasons, as a "bridge" to transplant in patients who qualify for an organ but would not survive the wait otherwise, as a "bridge" to recovery in patients who are expected to recover ventricular dysfunction after resolution of another disorder such as myocarditis, and as an alternative to transplant (i.e., destination therapy) in patients who do not qualify for a new organ. [313]

Additionally, now, there are two types of "artificial hearts" available for use in the place of VAD therapy. The CardioWest® requires the patient to stay at the hospital because of the size of the control panel and the external power source. The AbioCor® is an entirely implantable device with a small battery that provides power through the skin and was designed as an alternative to transplant with the goal of becoming an effective destination therapy. [314]

2.4.5 OUTCOMES/PROGNOSIS

The mortality of chemotherapy-induced heart failure appears to display a similar trend to heart failure of other etiologies; patients that are symptomatic at the time of diagnosis realize worse outcomes than those patients that are asymptomatic at time of diagnosis. Haq and colleagues performed a retrospective chart review of adult patients diagnosed with heart failure subsequent to exposure to doxorubicin therapy. All patients that met inclusion criteria were in NYHA classes II – IV and were split into two groups

[313] John G.T. Augoustides and Hynek Riha, "Recent Progress in Heart Failure Treatment and Heart Transplantation," *Journal of Cardiothoracic and Vascular Anesthesia* 23, no. 5 (October 2009): 738–748.

[314] Nicolini and Gherli, "Alternatives to Transplantation in the Surgical Therapy for Heart Failure."

depending on whether CHF was controlled at time of death (group I (n = 18), group II (n = 25)) and group I was further subdivided into three groups based on the patients' response to heart failure therapy. There were 43 patients included in the study, all but four patients developed symptoms of heart failure within six months of their last dose of doxorubicin. Of the included patients, 18 died as a result of heart failure (group I = 12, group II = 6). [315]

These authors concluded that symptom severity is a predictor of poorer prognosis, patients in NYHA classes III or IV had significantly worse survival than those patients in NYHA class II (p = 0.05). The authors also mention that patients may recover some cardiac function with appropriate drug therapy, although damage is not considered reversible. [316] These results support the idea that monitoring and prevention is a worthwhile strategy to improve outcomes.

In another retrospective chart review of nineteen patients diagnosed with anthracycline-induced heart failure, Moreb and Oblon sought to examine long-term outcomes. The authors divided the patients into two groups; those who died from CHF were in group one (n = 7), those who survived in group two (n = 12). Response was defined using the NYHA classification system. Of the patients in group two, three had a complete response, eight patients improved and one had stable CHF with follow-up time ranging from two to eight years. The authors found a statistically significant association between NYHA class and mortality, patients in class III or IV tended toward worse outcomes (p = 0.065). [317]

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[315] Haq et al., "Doxorubicin-induced Congestive Heart Failure in Adults."
[316] Ibid.
[317] Moreb and Oblon, "Outcome of Clinical Congestive Heart Failure Induced by Anthracycline Chemotherapy."

The authors also noted that all of the patients in group one received cumulative doxorubicin doses ≥ 300 mg/m^2, however, five of the patients in group two received cumulative doses less than 300 mg/m^2 indicating that although cumulative dose is considered the most significant risk factor, heart failure can occur at a wide range of doses. These authors did not find a significant association with any other factors, although, they do suggest that larger studies may be better able to explore those factors. [318]

Since treatment of early, asymptomatic disease has been shown to improve long term outcomes in heart failure patients, a study was conducted to determine whether outcomes differed between patients with class I heart failure and patients with asymptomatic LV dysfunction. Those with class I heart failure must have had prior history of congestive symptoms for inclusion. It was found that for those patients with asymptomatic LV dysfunction, short-term outcomes were better (100% survival at two years), however, long-term survival was not significantly different in the class I heart failure group with seven year mortality ~50%. [319]

2.4.6 ECONOMIC IMPLICATIONS

A recent retrospective chart review by Choi and colleagues examined the risk and cost of anthracycline cardiotoxicity. There were three patient groups, those patients who received anthracycline chemotherapy (ACC) (n = 3,428), patients who received a non-anthracycline chemotherapy (NACC) regimen (n = 7,125) and a control group who did not receive chemotherapy (n = 10,553). The authors used the first chemotherapy claim as

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[318] Ibid.

[319] Margaret M. Redfield et al., "Natural History of Incidentally Discovered, Asymptomatic Idiopathic Dilated Cardiomyopathy," *The American Journal of Cardiology* 74, no. 7 (October 1, 1994): 737–739.

the index date and patients were followed for 24 months, cardiac event (CE) was determined using ICD-9 codes. [320]

The investigators found that the ACC group had higher rates of CE over the follow-up period starting as early as month three. At 12 months, the ACC group had 485 patients with a cardiac event (14%), the NACC group had 381 (5%) and the control group had 310 (3%). This gave an OR of 3.98 and 1.31 for the ACC and NACC groups respectively. The mean costs for each group were $59,287, $20,528, and $11,600 for the ACC, NACC and controls respectively, showing that groups with higher numbers of cardiac events incur greater cost to the health system. [321]

In a much older economic analysis of the toxicity secondary to anthracyclines, the authors compared the number of cardiotoxic and febrile neutropenia events, hospitalizations and utilization of resources between patients receiving doxorubicin (FAC) and epirubicin (FEC) for the treatment of breast cancer. The study was a retrospective chart review, data for cardiotoxic events included the number of monitoring procedures that were ordered, occurrence of an event requiring a hospitalization, length of hospital stay, supportive care required, number of cardiology consultations. Patients with previous cardiovascular event (CHF or MI) were excluded. [322]

The economic analysis was performed from the institutional perspective, the study was conducted in Canada using the incidence method and results were reported in Canadian dollars. The resultant costs were reported as overall cost per incident and costs per cycle of therapy. For medication costs, the authors used the hospital's ordering cost

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[320] J. C Choi et al., "Risk and Cost of Anthracycline-induced Cardiotoxicity Among Breast Cancer Patients in the United States," *J Clin Oncol (Meeting Abstracts)* 27, no. 15S (2009): 1037–.

[321] Ibid.

[322] G. Dranitsaris and T. M. Tran, "Economic Analyses of Toxicity Secondary to Anthracycline-based Breast Cancer Chemotherapy," *European Journal of Cancer* 31, no. 13–14 (1995): 2174–2180.

plus the estimate of personnel cost of medication preparation and/or administration (excluding the costs of the chemotherapy regimens because they were considered equivalent). The costs for daily hospitalization were obtained from the Ontario Hospital Association and the costs for laboratory and diagnostic tests were obtained from their respective departments. The authors found that the costs of cardiotoxic events per episode were $4,268.08 and $2,447.28 for the FAC (n = 5) and FEC (n = 2) groups respectively. When the costs for cardiotoxic events were adjusted for the difference in the number of courses received, those costs were $80.77 and $51.90 for the FAC and FEC groups respectively (p = 0.68). [323]

2.5 Summary of Chapter Two

An unfortunate consequence of cancer treatment is the possibility of long-term effects from the therapy. This is often seen in patients treated for breast cancer with anthracyclines and/or trastuzumab. A continuing challenge is that toxicity cannot be accurately predicted and since the exact mechanism of cardiotoxicity subsequent to anthracycline or trastuzumab is not known it cannot be effectively prevented.

Clinical practice has attempted to be proactive regarding the issue of cardiotoxicity through the development of preventive or protective strategies, however, patients still develop this condition. There are data that suggest anthracycline analogs, liposomal or pegylated formulations and protective agents can be useful in the prevention of heart failure secondary to cancer treatment, however, even when treated with these agents, patients still have a risk of heart failure. Additional strategies such as limiting

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[323] Ibid.

cumulative dose, increasing infusion time, and changing dosing schedules have also failed to eliminate this problem.

Patients that develop heart failure are typically diagnosed in the clinical or symptomatic stages and are prone to higher mortality rates than patients who are diagnosed in earlier stages. More efficient strategies for long-term monitoring are needed to enable earlier detection and diagnosis.

CHAPTER THREE: DETECTION OF CARDIOTOXICITY

3.1 Introduction

Improvements in technology have afforded earlier detection of cancer which increases success of treatment thus improving overall survival. The age-adjusted ten-year survival for breast cancer, lymphoma and testicular cancer is 70%, 80% and 90% respectively. [324] Monitoring for adverse events has become increasingly important as improvements in therapy and screenings are realizing higher survival rates. Addition of several monoclonal antibodies can increase the cardiotoxicity of several regimens and the use of anthracyclines with platinum agents also increases toxicity, whereas platinum agents alone have very low cardiotoxicity. [325]

It is recommended that close monitoring of these patients be performed, however, concrete guidelines have yet to be developed. It is also recognized that monitoring is especially important in patients who have received agents that are known to cause cardiac dysfunction, such as anthracyclines, trastuzumab and radiation, or the combination of all three. Again, current treatment and surveillance guidelines do not give specific recommendations on the best techniques. Monitoring during therapy can assist in decisions as to whether to continue chemotherapy to maximize efficacy to eradicate tumor burden. [326]

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[324] Renske Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment: Strategies for Early Detection," *The Lancet Oncology* 10, no. 4 (April 2009): 391–399.

[325] Ibid.

[326] P. J. Barrett-Lee et al., "Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk," *Ann Oncol* 20, no. 5 (May 1, 2009): 816–827.

There are a handful of guidelines that recommend monitoring cardiac function of patients receiving cardiotoxic therapy. Available guidelines do not necessarily include all of the elements needed to guide monitoring and often do not include recommendations for long-term follow-up. [327] Since toxicity has a strong relationship to cumulative dose, the recommended monitoring frequencies are often dose-driven. There appears to be differences in sensitivities between patients with regards to the cumulative dose that is tolerated, therefore, there is no minimum dose anthracyclines that prevents cardiotoxicity for all patients.

When monitoring for anthracycline-induced cardiotoxicity, it is typically recommended at the beginning of therapy, after administration of half the total anthracycline cumulative dose, and before every subsequent dose. It is also recommended that during follow-up, left ventricular ejection fraction (LVEF) evaluation occur at three, six, and 12 months after the end of treatment. [328] The generally accepted "rule-of-thumb" for when treatment should be suspended is if there is a decline of LVEF by more than 10% associated with an absolute LVEF value of less than 50%. [329] However, when monitoring cardiac function via LVEF, toxicity may not be apparent until almost 2/3 of what is considered the recommended safe dose (RSD) has been received (the RSD for doxorubicin is 450 mg/m^2). [330]

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[327] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment"; ibid.

[328] Ping Lu, "Monitoring Cardiac Function in Patients Receiving Doxorubicin," *Seminars in Nuclear Medicine* 35, no. 3 (July 2005): 197–201; R. G Schwartz et al., "Congestive Heart Failure and Left Ventricular Dysfunction Complicating Doxorubicin Therapy: Seven-year Experience Using Serial Radionuclide Angiocardiography," *The American Journal of Medicine* 82, no. 6 (1987): 1109–1118.

[329] Lu, "Monitoring Cardiac Function in Patients Receiving Doxorubicin."

[330] Michael S. Ewer and Robert S. Benjamin, "Formulae for Predicting the Likelihood of Developing Congestive Heart Failure Following Anthracycline Chemotherapy: Added Evidence for Early Cardiotoxicity," *Journal of Cardiac Failure* 11, no. 6, Supplement 1 (August 2005): S159.

Schwartz and colleagues conducted an investigation in which guidelines for monitoring patients receiving doxorubicin were developed, patients were categorized based on whether follow-up was conducted in concordance or discordance with the guidelines and cardiac outcomes were subsequently compared. The monitoring parameters were based on published research and clinical experience. The guidelines used in the study included baseline (prior to receiving doxorubicin dose of 100 mg/m^2) evaluation of LVEF using radionuclide angiocardiography (RNA), this result determined the schedule of the subsequent scans (LVEF $\geq$ or $< 50\%$). For the patients with a normal baseline LVEF ($\geq 50\%$), the second study was performed after 250 – 300 mg/m^2, repeated after 400 mg/m^2 or 450 mg/m^2 in patients with risk factors or without risk factors respectively and prior to each dose thereafter. Doxorubicin was to be discontinued if LVEF decreased $> 10\%$ to value $\leq 50\%$. For patients with baseline LVEF $\leq 30\%$, doxorubicin should not be started, for LVEF between 30 - 50%, patients received a scan prior to each dose, doxorubicin was discontinued if LVEF decreased $> 10\%$ to value $\leq$ 30%. [331]

Patients were considered high-risk (n = 282) if they met one of three criteria, if their LVEF declined by more than 10% to an absolute value of $\leq 50\%$, cumulative dose of doxorubicin of ≥ 450 mg/m^2, or abnormal baseline LVEF. Heart failure developed in 16% (n = 46) of high-risk patients with 21 (46%) mild, 19 (41%) moderate, and five (11%) severe cases; there was one death attributed to heart failure (cardiogenic shock). Development of heart failure did not differ between patients with or without abnormal baseline LVEF. Authors considered heart failure "predicted" if LVEF decreased $\geq 10\%$ to a value of $\leq 50\%$ and heart failure resulted after the administration of doxorubicin that

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[331] Schwartz et al., "Congestive Heart Failure and Left Ventricular Dysfunction Complicating Doxorubicin Therapy."

followed that decrease. High-risk patients were categorized based on adherence to the prescribed guidelines and outcomes were compared between groups. Group A (n = 70) had follow-up that was in accordance with guidelines and had two patients that developed heart failure, both were mild cases, whereas Group B (n = 212) had 44 (20.8%) patients that developed heart failure (p < 0.001). The authors concluded that these results suggest serial RNA has utility in monitoring and preventing heart failure and that guideline adherence was effective for prevention and limiting severity in high-risk patients. [332]

When HER-2 positive patients are to receive trastuzumab therapy, there are additional recommendations for monitoring developed as a result of findings from the HERA Trial.[333] There is a baseline evaluation similar to all patients and assessment of LVEF by either MUGA or ECHO. It is recommended that LVEF be measured after the completion of chemotherapy and before the initiation of trastuzumab. The patient must have LVEF above the lower limit of normal (LLN) of the institution for trastuzumab to be started. For patients who start trastuzumab, LVEF is re-evaluated at four and eight months, and at the conclusion of therapy for any patient who required any cardiovascular treatment during therapy. For those who needed therapy postponed, LVEF is re-evaluated in three months. If at any time during treatment, the patient develops symptoms suggestive of heart failure or LVEF is ≤ 40%, trastuzumab should be suspended. (Figure 3.1) [334]

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[332] Ibid.

[333] Thomas M. Suter et al., "Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial," *J Clin Oncol* 25, no. 25 (2007): 3859–3865.

[334] A L Jones et al., "Management of Cardiac Health in Trastuzumab-treated Patients with Breast Cancer: Updated United Kingdom National Cancer Research Institute Recommendations for Monitoring," *British Journal of Cancer* 100, no. 5 (2009): 684–692.

Figure 3.1 Proposed Monitoring Strategies for Patients Receiving Trastuzumab[335]
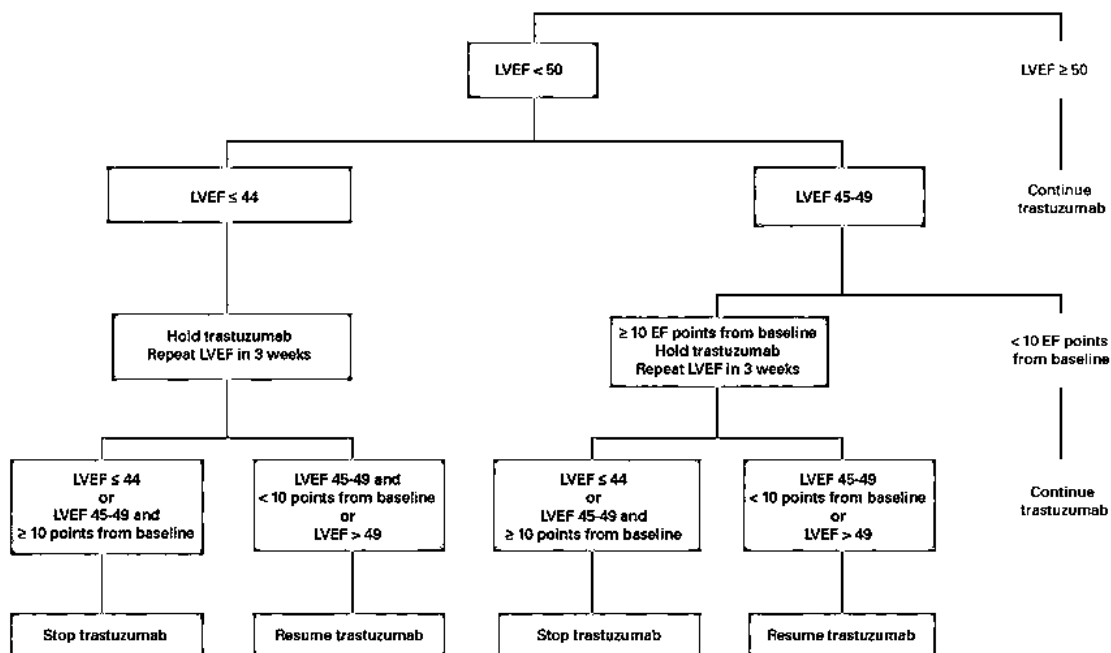
Both ASCO and the ACC/AHA have guidelines that mention monitoring cardiac function in patients receiving doxorubicin, however, in the case of ASCO, it is only with respect to patients already receiving dexrazoxane for cardioprotection. ASCO does not make any mention of monitoring strategies in patients who are not receiving dexrazoxane. [336] The AHA/ACC guidelines for diagnosis and management of heart failure lists anthracyclines as a risk factor, thus these patients would classify as stage A. It also states that these patients should be monitored closely and that the use of dexrazoxane

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[335] Suter et al., "Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial."

[336] Lynn M. Schuchter et al., "2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology," *J Clin Oncol* 20, no. 12 (June 15, 2002): 2895–2903.

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could potentially be beneficial. [337] There are guidelines for the use of RNA and ECHO developed by the American Society of Nuclear Cardiology and American Society for Echocardiography respectively.[338] These guidelines provide recommendations for the frequencies of scans; however, there is little information given on the course of action to take when tests are abnormal.

Monitoring is important since the earlier left ventricular dysfunction is discovered; the sooner patients can begin drug therapy to reverse the remodeling process. [339] This is true for patients with symptomatic or asymptomatic dysfunction and it has been shown that patients who are symptomatic would benefit from receiving conventional heart failure therapies such as ace-inhibitors and beta blockers [340] There are a number of barriers that potentially inhibit the suggested frequency of monitoring of patients in routine clinical practice (outside of a trial setting). The costs of monitoring utilizing "preferred" or common methods are high; as a result, patients may not receive routine monitoring at regular intervals (if at all). Therefore, it is necessary to explore other options in monitoring of cardiac function; one algorithm was proposed by Clerico and colleagues (Figure 3.2).

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[337] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation"; ibid.

[338] Francis J. Klocke et al., "ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging—Executive Summary," *Circulation* 108, no. 11 (2003): 1404 –1418; Melvin D. Cheitlin et al., "ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)," *Circulation* 108, no. 9 (September 2, 2003): 1146–1162.

[339] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

[340] Brian R. J. Healey Bird and Sandra M. Swain, "Cardiac Toxicity in Breast Cancer Survivors: Review of Potential Cardiac Problems," *Clinical Cancer Research* 14, no. 1 (January 1, 2008): 14 – 24.

Figure 3.2 Proposed Algorithms for Evaluating Patients with Suspected LV Dysfunction [341]

Suspected LV dysfunction because of signs

Suspected HF because of symptoms and signs

Assess presence of cardiac disease by ECG, X-ray or natriuretic peptides (where available) → Normal HF or LV dysfunction unlikely

Test abnormal

Normal HF or LV dysfunction unlikely ← Imaging by echocardiography (nuclear angiography or MRI) where available

Test abnormal

Assess aetiology, degree, precipitating factors and type of cardiac dysfunction

Additional diagnostic tests where appropriate (e.g. coronary angiography)

Choose therapy

LV: Left-Ventricular; HF: Heart Failure; ECG: Electrocardiogram; MRI: Magnetic Resonance Imaging

[341] Aldo Clerico et al., "New and Emerging Biomarkers of Heart Failure," *Critical Reviews in Clinical Laboratory Sciences* 46, no. 3 (2009): 107–128.

3.2 Methods of Detection

Early detection and treatment of heart failure from chemotherapy or other etiologies can reduce development of clinical manifestations. There are a number of different methods that could be utilized to monitor patients for the development of cardiotoxicity; these include invasive methods such as biopsies, radiological methods such as echocardiograms (ECHO) and multiple-uptake-gated acquisition (MUGA) scanning (multi-gated acquisition scan), electrocardiograms (ECG's), and laboratory values such as cardiac troponins and natriuretic peptides.[342] The table below lists the available methods with their respective advantages and disadvantages. (Table 3.1)

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[342] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment"; Jones, Swanton, and Ewer, "Anthracycline Cardiotoxicity."

Table 3.1 Advantages and Disadvantages of Methods to Detect Cardiotoxicity[343]

Method	Advantages	Disadvantages
Biopsy	Provides Histological Evidence	Invasive Requires specialist Small sample is tested
ECG	Highly Available/ Non-Invasive Computerized analysis Prolonged QT_c interval possible marker of cardiotoxicity	Doesn't provide information on LV function QT_c interval is the only investigated marker Variation in intra-observer interpretation Timing of ECG changes is not known
MUGA	Well established/ validated method Assesses regional wall motion and diastolic function Low intra-individual and intra-observer variability High Sensitivity to anthracycline damage	Exposes patient to radiation Not sensitive to early changes in LVEF No information on valve function Low spatial resolution, High cost Limited information on diastolic function
ECHO	Provides wide spectrum of information Does not expose patients to radiation Tissue Doppler imaging may improve detection of dysfunction	Image quality limits use in some patients LVEF not sensitive for detection of early disease Time consuming, High intra-individual and intra-observer variability; Some parameters are dependent on preload
Biomarkers	Highly Available; Minimally Invasive Easy Analysis/Interpretation Low Intra-observer variability	Data regarding clinical use is limited Exact Predictive Value Not Certain Positive/Negative Values not yet defined
MRI	Can assess myocardial damage and function Gives high-quality, detailed image Reliable calculation of LVEF	Limited availability, High cost Unknown whether early damage can be visualized Contraindicated in those with metal implants
CT	Image quality similar to MRI Low temporal resolution	High radiation dose Limited availability

LV: Left Ventricular; LVEF: Left Ventricular Ejection Fraction; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; ECG: Electrocardiogram; ECHO: Echocardiogram; MUGA: Multi-Gated Acquisition Scan; QT_c: Corrected QT interval duration

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[343] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

3.2.1 BIOPSIES

Biopsies were used in the past and are considered the "gold standard" in monitoring of cardiotoxicity as it is often considered the most reliable and specific means of detection. Anthracyclines in particular, cause a specific histological pattern of damage to myocytes, and these patterns have been shown to mirror clinical findings in animal models and in practice. [344] Biopsy provides histological evidence that cannot be provided through any other means. However, because of the nature of the sampling (damage is typically not uniform throughout myocardium); there is potential for a negative biopsy when there is damage present. Additionally biopsies lack any indication of the patients' clinical status or myocardial function. These limitations decrease the utility of biopsy in this setting, as well as the resources required and invasiveness of the procedure. [345]

Benefits to biopsy include that it is very specific and sensitive to changes and is considered to be the most reliable method, however there are high costs associated with this test since the procedure is done through a cardiac catheter and involves interpretation by a specialist. Additionally, the use of biopsy to detect changes in this patient group has had reports of false negative result. One study found negative results in about 1/3 of patients (7 of 20) with clinical symptoms of heart failure; these investigators also found that of the 44 patients that did not have clinical signs of toxicity, 23 had histological signs of toxicity. These authors calculated a sensitivity and specificity of histological evaluation of 65% and 48% respectively and concluded that although their study confirmed previous results regarding the risk factors of anthracycline use and

[344] Speyer, Kobrinsky, and Ewer, "Cardiac Effects of Cancer Therapy."
[345] Barrett-Lee et al., "Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk."

cardiotoxicity, monitoring patients with biopsy has limited utility since toxicity could not be accurately predicted with histological changes. [346]

Ideally, a monitoring method would be able to detect cardiac changes early enough that intervention could provide benefit and this is not true of biopsy, as histological changes are often visible late and therefore remodeling would be difficult to reverse. [347] Although biopsy results have been shown to correlate well with left ventricular function measured by other methods such as ECHO, and has been shown to detect damage; it has not been able to predict which patients would experience toxicity. Additionally, considering the risk involved with repeated testing and concerns with safety, biopsy has had limited utility as a monitoring tool. [348]

There are guidelines in place for interpretation of biopsy results with regard to the degree of heart failure (Table 3.2) and the scale has been shown to correlate well with dose-dependent damage and left ventricular function as measured by other methods. [349]. Currently, biopsy is rarely done in favor of less invasive monitoring methods (such as radiological procedures or lab tests) that do not require the same level of specialist input in performing the procedure and interpreting the results. [350] Current ACC/AHA

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[346] Jeffrey M. Isner et al., "Clinical and Morphologic Cardiac Findings After Anthracycline Chemotherapy: Analysis of 64 Patients Studied at Necropsy," *The American Journal of Cardiology* 51, no. 7 (April 1983): 1167–1174.

[347] Jerry D Glickson, John R Forder, and John C Chatham, "Imaging of Cardiotoxicity," *Molecular Imaging: Official Journal of the Society for Molecular Imaging* 7, no. 3 (June 2008): 115–117.

[348] Victor J. Ferrans and William C. Roberts, "Myocardial Biopsy: A Useful Diagnostic Procedure or Only a Research Tool?," *The American Journal of Cardiology* 41, no. 5 (May 1, 1978): 965–967.

[349] M. R. Bristow, J. W. Mason, and J. R. Daniels, "Monitoring of Anthracycline Cardiotoxicity," *Cancer Treatment Reports* 62, no. 10 (October 1978): 1607–1608; Bristow et al., "Efficacy and Cost of Cardiac Monitoring in Patients Receiving Doxorubicin"; G. Takemura and H. Fujiwara, "Doxorubicin-induced Cardiomyopathy from the Cardiotoxic Mechanisms to Management," *Progress in Cardiovascular Diseases* 49, no. 5 (2007): 330–352.

[350] Barrett-Lee et al., "Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk"; Speyer, Kobrinsky, and Ewer, "Cardiac Effects of Cancer Therapy."

guidelines do not recommend the use of biopsy in the diagnosis or monitoring of heart failure patients. [351]

Table 3.2 Histopathologic Scale of Anthracycline-Induced Cardiac Toxicity[352]

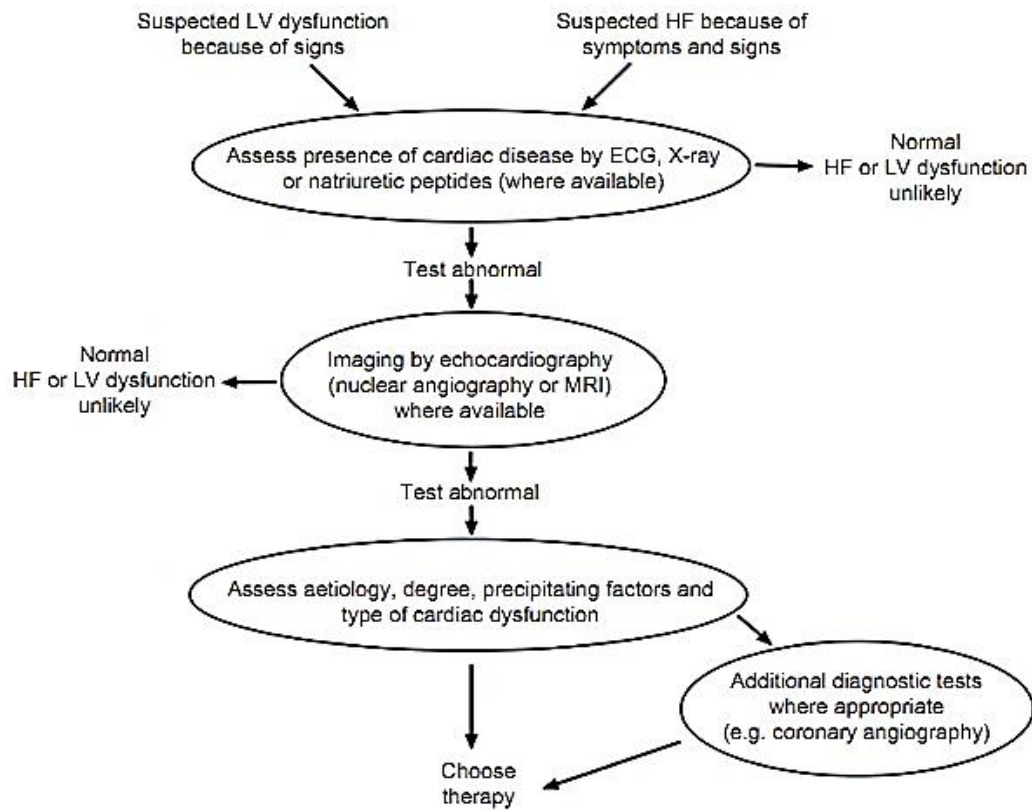| Grade	Features
0	Within normal limits
1	Minimal number of cells ($< 5\%$) showing change (such as early myofibrillar loss or distended sarcoplasmic reticulum)
1.5	Small group of cells involved (5 - 15%) some of which have a definite change (such as marked myofibrillar loss or cytoplasmic vacuolization)
2	Group of cells (16 - 25%) some of which have a definite change (such as marked myofibrillar loss or cytoplasmic vacuolization)
2.5	Group of cells (26 - 35%) some of which have a definite change (such as marked myofibrillar loss or cytoplasmic vacuolization)
3	Diffuse cell damage ($> 35\%$ of cells) with marked change (total loss of contractile elements or organelles; mitochondrial and nuclear degeneration)

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[351] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

[352] Bristow, Mason, and Daniels, "Monitoring of Anthracycline Cardiotoxicity."

3.2.2 ECG

Electrocardiogram (ECG) is a recording of electrical activity within the heart and the leads attached to patients' extremities and chest wall are able to detect instantaneous differences in electrical potentials. ECG can provide information that is essential to the diagnosis and treatment of many cardiac problems, and is the most widely used test in cardiac screening. The advantages of this test as a screening/monitoring tool lie in its wide availability and low cost. [353]

A variety of ECG changes have been reported with anthracycline use. These can include non-specific T- wave or ST-wave changes, low QRS voltage, prolongation of QT interval or ventricular arrhythmias. [354] The QT interval is the most often studied parameter with respect to anthracycline cardiotoxicity. ECG values automatically print out and display with currently available technology, which is a feature that also makes it easy to compare to previous testing [355] Patients with early ECG changes usually only suffer from acute and sub-acute symptoms that are transient in nature. [356] Anthracyclines, however, can cause arrhythmias in the chronic toxicity time period. It is not known if ECG monitoring would provide improved outcomes for these patients. However, prolonged QT-interval dispersion has been shown to predict heart failure in patients receiving cyclophosphamide. [357] QT dispersion is defined as the difference

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[353] Agustin Castellanos, Alberto Interian Jr., and Robert J. Myerburg, "The Resting Electrocardiogram," in *Hurst's the Heart*, ed. Valentin Fuster (New York: McGraw-Hill Medical, 2008), Chapter 13; Rick A. Nishimura et al., "Non-Invasive Cardiac Imaging: Echocardiography, Nuclear Cardiology and MRI/CT Imaging," in *Harrison's Principles of Internal Medicine* (New York: McGraw-Hill Medical, 2008).

[354] W Rhoden, P Hasleton, and N Brooks, "Anthracyclines and the Heart.," *Heart* 70, no. 6 (1993): 499–502.

[355] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

[356] Rhoden, Hasleton, and Brooks, "Anthracyclines and the Heart."

[357] M. Galderisi et al., "Cancer Therapy and Cardiotoxicity: The Need of Serial Doppler Echocardiography," *Cardiovascular Ultrasound* 5, no. 1 (2007): 4.

between the longest and shortest QT interval in an ECG. Nakamae and colleagues conducted a study specifically aimed at determining if there were relationships between QT dispersion/corrected QT (QTcD) dispersion and diastolic and systolic parameters as measured by ECHO. [358]

The investigators enrolled 79 patients receiving anthracycline therapy for hematologic malignancies and along with 44 healthy controls. QT dispersion was measured both automatically and manually. Additionally, to assess reproducibility of the automatic measure of QTcD, five of the healthy controls had ten automatic measurements of QTcD; this yielded a coefficient of variance (CV) of 5.2%. There was a significant relationship between automatic and manual measures of both QT dispersion ($r = 0.82$, $p < 0.001$) and QTcD ($r = 0.81$, $p < 0.001$). [359]

There were significantly higher QTcD values in the anthracycline group when compared to the healthy controls (52.2 ± 14.9 vs. 43.7 ± 10.1 msec. $p = 0.001$) and there was a significant correlation found between QTcD and cumulative dose ($r = 0.28$, $p = 0.02$). Additionally, there were significant correlations found between QTcD and mean LV end-diastolic ($r = 0.35$, $p < 0.01$) and systolic diameters ($r = 0.43$, $p < 0.01$). However, when compared to specific measures of systolic or diastolic function, QTcD only had significant relationships with LVEF ($r = -0.46$ $p < 0.001$) and FS ($r = -0.27$, $p = 0.02$), which are both measures of systolic function. These authors concluded that although their results did not confirm relationships with any diastolic functional parameters, they believe that these results cannot necessarily deny relationships between

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[358] Hirohisa Nakamae et al., "QT Dispersion Correlates with Systolic Rather Than Diastolic Parameters in Patients Receiving Anthracycline Treatment," *Internal Medicine* 43, no. 5 (2004): 379–387.
[359] Ibid.

these parameters since ECHO is a poor measure of early diastolic dysfunction. They therefore concluded that further study was required. [360]

In a small study of 26 leukemia patients who received anthracycline therapy, ECG and ECHO findings were compared. All patients received an ECG at baseline, after the first chemotherapy dose, after the last dose and six months after the conclusion of therapy. Parameters documented by the researchers included: heart rate, RR interval, PQ interval, QRS duration, and QT interval, total QRS voltage in limb leads, presence of repolarization changes, arrhythmias or other abnormalities. Each ECG was performed and read by two physicians and ECHO's were done at the same times the ECG's were performed. The authors found a significant correlation between QRS voltage and both systolic ($r = 0.66$, $p < 0.001$) and diastolic ($r = 0.592$, $p < 0.01$) LV dysfunction shown on ECHO. There were also significant correlations between QT prolongation and both systolic ($r = 0.246$, $p < 0.01$) and diastolic ($r = 0.257$, $p < 0.01$) LV dysfunction shown on ECHO. Additionally, patients with prolonged QTc were at risk for ventricular arrhythmias and sudden death. The authors concluded that larger studies would need to be conducted to examine the utility of ECG monitoring. [361]

In a slightly larger, yet much older, study enrolled 49 patients who received doxorubicin and 20 control patients who had cancer but were treated with other chemotherapy regimens. A minimum of four ECG's were evaluated for each patient. An ECG recorded within one month prior to starting doxorubicin was considered the baseline in the study group and ECG prior to chemotherapy was baseline for the controls. Doxorubicin patients were stratified based on the cumulative dose received. Changes in

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[360] Ibid.

[361] J M Horacek et al., "Assessment of Anthracycline-induced Cardiotoxicity with Biochemical Markers," *Experimental Oncology* 29, no. 4 (December 2007): 309–313.

QRS duration and ventricular conduction patterns were not significantly different between groups. These authors therefore concluded that ECG had limited utility in screening patients in this setting and that screening should include better tests of ventricular function. [362]

There was a recent meta-analysis of four studies examining the use of ECG in patients suspected of HF (non-cancer patients) referred for ECHO (n = 1419). The authors calculated the sensitivity and specificity of abnormal ECG to identify LV systolic dysfunction for each study. The sensitivity for the four studies ranged from 73 to 94% and failure to detect patients with LV systolic dysfunction ranged from 6% to 27% (average of 16%). The authors extrapolated an ROC value of 0.84 for the four studies, which is the true positive rate. The authors concluded that their results confirmed previous results that ECG in inadequate when used as a screening tool in patients who are suspected of having heart failure and are referred for an ECHO. [363]

Since it is primarily non-specific ECG changes seen in anthracycline use, the test is non-specific , the false negative rate is high, and a predictive role has yet to be established, Therefore, using ECG has not proven to be useful for monitoring/screening in this clinical circumstance. [364]

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[362] Sandra K. Weaver et al., "A Paucity of Chronic Electrocardiographic Changeswith Adriamycin Therapy," *Journal of Electrocardiology* 11, no. 3 (1978): 233–238.

[363] K Khunti et al., "Accuracy of a 12-lead Electrocardiogram in Screening Patients with Suspected Heart Failure for Open Access Echocardiography: a Systematic Review and Meta-analysis," *European Journal of Heart Failure* 6, no. 5 (2004): 571–576.

[364] Rhoden, Hasleton, and Brooks, "Anthracyclines and the Heart."

3.2.3 RADIOLOGICAL PROCEDURES

Radiological procedures are less-invasive methods for monitoring. These can include radionuclide ventriculography or multiple uptake gated acquisition scan (MUGA), echocardiography (ECHO), more advanced ECHO procedures like two-dimensional ECHO with Doppler and stress echocardiography, CT scan, MRI and scintigraphy. These procedures typically are performed to provide information regarding the patients LVEF, which is considered the parameter of choice since HF patients' mortality is inversely proportional to LVEF. Radiological procedures are popular choices for monitoring patients because of accessibility, availability of scans and familiarity with the procedures; however, these tests tend to be more expensive than laboratory monitoring techniques and more resource intensive with respect to scheduling and interpretation. Additionally, they are used more often in the trial setting than in regular clinical practice. Serial measurements are necessary and have to be compared to baseline values to determine if there are clinically relevant changes after therapy. [365]

Typically when utilizing radiological procedures for monitoring or screening the LVEF is the most common parameter used to assess cardiac function during cancer therapy. LVEF is a ratio of the stroke-volume (which is the difference between the LV end-diastolic and end-systolic volumes) to the end-diastolic volume, [SV/EDV] multiplied by 100 to yield a percent. LVEF is a measure of systolic function and considered the best global indicator of such. LVEF can underestimate the actual damage because there is a compensatory mechanism in early dysfunction via a reserve in the myocardium that can maintain output although there are damaged myocytes. This can be problematic if LVEF is the only parameter used to assess cardiac function as a normal

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[365] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

LVEF can mask actual damage as diastolic dysfunction can be present without systolic dysfunction and as many as 30 - 40% of patients presenting with heart failure have normal LVEF. [366] In addition, research has shown that determination of LVEF is not sensitive or specific enough to predict heart failure post-chemotherapy; there are data that suggests that drops in LVEF shown on ECHO or MUGA scans are indications of later, more significant damage. [367]

3.2.3.1 ECHO

Echocardiography is a safe and widely available procedure for use in patients with known or suspected heart failure. There are a number of different types of echocardiography procedures that can be used in diagnosing or monitoring heart failure, those include two- and three- dimensional scans, Doppler and stress ECHO's. The table below illustrates the different types of ECHO's and what each type is used for. [368] A benefit of using ECHO instead of methods such as radionuclide ventriculography is that ECHO does not utilize radiation in the scan and gives a number of functional parameters (both systolic and diastolic) that are not available with radionuclide ventriculography. While ECHO can give measures of diastolic and systolic function, diastolic measures are more sensitive to early changes in cardiac function. [369]

Expansion of the technology has made ECHO useful in a number of applications and there are now several types of ECHO scans that can be performed. These include:

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[366] Ibid.

[367] Barrett-Lee et al., "Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk."

[368] Antonio Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure," *Heart Failure Reviews* 8, no. 2 (April 1, 2003): 181–189.

[369] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

two-dimensional trans-thoracic ECHO, Doppler interrogation, Trans-esophageal echo, three-dimensional ECHO, and contrast ECHO. The basic two-dimensional ECHO utilizes ultrasonic reflections to visualize the structure of the heart. In trans-thoracic (TTE) ECHO, the principle is the same, and the transducer is placed on the chest wall. The images produced are immediate, which gives ECHO a distinct advantage over other imaging techniques, however, with the immediate images comes poor quality creating a major limitation. Doppler ECHO also uses the same type of ultrasound technology but the reflections are from blood cells instead of the heart itself, in order to measure blood flow/velocity. Tissue Doppler ECHO measures the velocity of myocardial motion which gives a type of measure for contraction and relaxation. [370] A benefit of three-dimensional over two-dimensional ECHO is the ability to depict cardiac structures as they exist in three-dimensional space, therefore eliminating the need for modeling and the use of assumptions to determine the functional parameters of interest. [371]

While ECHO is a non-invasive procedure, widely available and accessible, and often able to detect etiologies of heart failure, there are limitations to the use of ECHO in diagnosing patients with HF, which include the dependability of the operator and assumptions regarding the baseline dimensions of the left ventricle. [372]

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[370] Nishimura et al., "Non-Invasive Cardiac Imaging: Echocardiography, Nuclear Cardiology and MRI/CT Imaging."

[371] Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure."

[372] Ibid.

Table 3.3 Types of ECHO and Uses in Heart Failure[373]

Type of ECHO	Used to Detect
Routine Use	
Two-Dimensional	Anatomical and/or functional cardiac abnormalities
Doppler	Valvular or diastolic function, shunts, intracardiac gradient assessment
Trans-Esophageal	Visualize cardiac structures when transthoracic ECHO is limited, used when visualization of posterior of heart and great vessels is needed
Stress	Exercise: assessment of ischemia Dobutamine: viability: evaluation of contractile reserve, ischemia assessment, stunned and/or hibernating myocardium Doppler: physiologic information related to symptoms in patients with concomitant valvular disease
Experimental Use	
Three-Dimensional	More accurate assessment of cardiac structures; removes geometric assumptions required for 2-D ECHO
Tissue Doppler	Able to detect abnormal patterns to mitral inflow velocities
Contrast	Able to detect perfusion

Two-dimensional ECHO (trans-thoracic) is widely used to monitor cardiotoxicity. LVEF and fractional shortening (FS) are parameters obtained via two-dimensional ECHO that are used to evaluate systolic function. It has been shown that substantial damage is possible (i.e., diastolic dysfunction) before there is a notable decline in either FS or LVEF. [374] Other parameters that can be obtained via ECHO and used for monitoring include endocardial wall thickness, increasing isovolumic relaxation period, reduction in peak flow velocity which are diastolic parameters, all of which manifest sooner than changes in FS or LVEF. [375]

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[373] Ibid.

[374] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity."

[375] Ibid.

Parameters of interest includes the left ventricular ejection fraction [LVEF], two-dimensional ECHO can determine ejection fraction from modeling techniques using values for end systolic and diastolic volumes. This has shown to be consistent with other methods of determining LVEF. A normal value is considered to be ≥ 55 – 60%; and values ≤ 40% would warrant drug therapy according to current treatment guidelines. Diastolic parameters of interest include the E/A ratio which is a ratio of early to late peak atrial velocities. This is important because it has been shown that diastolic impairment is more evident in early toxicity, usually before systolic dysfunction can be detected. [376]

ECHO with Doppler imaging is able to detect changes in diastolic function before the overt symptoms of systolic dysfunction manifest themselves. [377] Doppler imaging gives the ability to visualize flow and therefore, adds the measurement of parameters other than those which simply quantify anatomy. Flow velocity is the most common method to evaluate diastolic compliance. The trans-mitral velocity profile provides two waves which correspond to the early phase of filling (E-wave) and the atrial contraction contribution to filling (A-wave), these values are represented by a ratio of E-wave to A-wave (E/A) and a normal value is ≥ 1.6. With normal function the E-wave is much larger, as the ability of the heart to pump normally becomes impaired, the value for E decreases and the pressure in the atrium increases, any value for the E/A Ratio that is < 1 is considered abnormal. [378]

Tissue Doppler Imaging (TDI) is a newer technique which permits an assessment of myocardial wall motion similar to traditional Doppler ECHO, however this technique is able to detect lower velocity frequency shifts. TDI also offers more objective measures

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[376] Audrey H. Wu, "Cardiotoxic Drugs: Clinical Monitoring and Decision Making," *Heart* 94, no. 11 (July 2008): 1503–1509.

[377] Ibid.

[378] Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure."

of function when compared to traditional ECHO which relies on a visual determination of parameters. TDI obtains parameters such as the velocity from early diastole, strain and strain rate which are all measures of diastolic function and less susceptible to intra-observer variability than the E/A ratio. [379] The addition of TDI could potentially add to the utility of ECHO in detection of clinical LV dysfunction, the use of ECHO to monitor cardiac toxicity is primarily during treatment and while TDI can detect the small changes in function, predictive value for heart failure after therapy has been concluded is not known. [380] There is increasing evidence that using ECHO to detect chemotherapy-induced heart failure has low sensitivity in the early stages when drug therapy can be most useful in reversing remodeling.

3.2.3.2   Other Imaging Procedures

Multi-gated Acquisition scanning (MUGA) is also known as radionuclide ventriculography, radionuclide angiography, and equilibrium radionuclide angiography. The procedure involves labeling the patients red blood cell pool with Tc-99m and imaging the movement of these cells through the chest as radioactive blood passes through the heart and vessels. Cells can be labeled by either injecting them directly or by "incubating" cells with the tracer then injecting them into the circulation. MUGA has shown to correlate well with LVEF obtained via catheterization (r = 0.94) [381]

MUGA is considered the "gold-standard" for evaluating LVEF, and with ECHO, are the most accepted methods of monitoring during therapy. Advantages include high

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[379] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

[380] Ibid.

[381] Peter G. Danias and Gary V. Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction," in *Up To Date* (Waltham, MA.: Up To Date, 2010), www.uptodate.com.

reproducibility and low intra- or inter-observer variability. Disadvantages include the exposure to radiation and low sensitivity to small changes that could be present in asymptomatic patients with early toxicity. [382]

Cardiovascular MRI or CT scanning are additional alternatives and can be performed to assess ventricular function. Cardiovascular MRI is considered the most accurate and precise non-invasive imaging technique to assess ventricular dysfunction. Some advantages of this technique include: a high resolution of the images, an ability to obtain images from any plane/orientation, an image not affected by patient's body habitus, no radiation or contrast needed, all aspects of anatomy and function can be evaluated, and consistent values for LVEF can be calculated. However there are disadvantages as well to the cardiovascular MRI; the test is not widely available, manual tracing of borders increases evaluation time and perhaps bias, artifacts may be created by any motion during imaging, it is uncomfortable for claustrophobic patients, and it cannot be performed at the bedside (unlike ECHO which can provide similar information). [383]

When combined with contrast, the cardiac MRI has been shown to detect subtle areas of myocardium with irreversible damage, however, evidence is lacking that would suggest this method has any gains over currently available technology. [384] CT scanning is widely available, reproducible and produces images with good delineation of myocardial borders. When compared to other methods such as cardiovascular MRI or MUGA, there have been mixed results, where some studies show good agreement in measurement of left and right ventricles, while other studies conclude that CT scanning overestimates

[382] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."
[383] Danias and Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction."
[384] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

LVEF. CT is usually not considered an optimal method to determine LVEF as patients are exposed to radiation during the procedure. [385]

The choice of scan is dependent on what the scan is meant to look for, as each has its own advantages and disadvantages. When measuring LVEF, the indication for testing is important as are the needs of the specific patients (i.e., importance of detecting even slight changes in LVEF). With regard to imaging, if it is critical to detect slight changes, serial measures using cardiac MRI or MUGA scanning are considered optimal. This is applicable to cancer patients, pre- and post-transplant patients and patients enrolled in clinical trials. [386]

3.2.4 LABORATORY PROCEDURES

Laboratory tests can be useful as they provide a non-invasive and inexpensive way to quantify a number of different processes with respect to cardiac function. Consequently, there are a number of laboratory tests that have been tested for use in monitoring cardiac function in cancer patients. The tests that have received the most study have been cardiac troponins and natriuretic peptides; however, there are others that have been proposed for use. These include serum lipid peroxide, serum carnitine, TNF-α, IL-6, IL-2, CA-125 and CRP. Utilizing laboratory methods in place of other more costly alternatives can potentially increase efficiency and cost-effectiveness of screening/diagnosis of heart failure. [387]

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[385] Danias and Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction."

[386] Ibid.

[387] I Shureiqi et al., "Clinical and Economic Impact of Multiple Gated Acquisition Scan Monitoring During Anthracycline Therapy," *British Journal of Cancer* 86, no. 2 (January 21, 2002): 226–232.

3.2.4.1   Biomarkers

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". [388] Biomarkers have proven to be valuable in a number of settings and can indicate a variety of health or disease characteristics such as genetic susceptibility or response likelihood, exposure types or levels, or subclinical or clinical responses to therapy. [389] Therefore, biomarkers have several different ways to provide utility in clinical practice, such as diagnosis and staging of disease, prediction of prognosis and monitoring responses to therapy. [390] As a result, they have a number of categories or classifications. These include antecedent, screening, diagnostic, staging, prognostic or therapeutic monitoring. [391]

Some characteristics of useful biomarkers are: they must be accurate, serial testing should be inexpensive and timely, they should provide information that would not be obtained from routine assessment, and the resulting value should assist in the subsequent care of the patient (Table 3.4). [392] Thus, no matter how markers are being used, if they are not affecting the management of the patient, they will not improve outcomes and will not likely be cost-effective. [393] Biomarkers can be measured from a

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[388] Arthur J. Atkinson et al., "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," *Clinical Pharmacology & Therapeutics* 69, no. 3 (March 2001): 89–95.

[389] Ramachandran S. Vasan, "Biomarkers of Cardiovascular Disease: Molecular Basis and Practical Considerations," *Circulation* 113, no. 19 (May 16, 2006): 2335–2362.

[390] Atkinson et al., "Biomarkers and Surrogate Endpoints."

[391] Clerico et al., "New and Emerging Biomarkers of Heart Failure"; Vasan, "Biomarkers of Cardiovascular Disease."

[392] Eugene Braunwald, "Biomarkers in Heart Failure," *New England Journal of Medicine* 358, no. 20 (2008): 2148–2159.

[393] Vasan, "Biomarkers of Cardiovascular Disease."

sample such as blood, urine or tissue, they can be recorded (ECG, BP, Holter monitor), or obtained via radiological procedures. [394]

Table 3.4 Characteristics and Corresponding Benefits of Ideal Biomarkers[395]

Administration	Interpretation
Accessible to patient	Adequate Analytical Sensitivity
Easy to Perform	High Degree of Diagnostic/Prognostic Accuracy
Automated	High Degree of Reproducibility
Low Cost	International Standardization
Favorable Cost-Benefit Ratio	Low Biological Variation
	Stability (both *in vivo* and *in vitro*)

When considering use of biomarker assays, one must consider the specific test characteristics such as the assay type, precision and performance relative to other means of detection and/or diagnosis. Assays can be point-of-care testing (POC) or rapid testing which may have different cut-off values from laboratory tests. [396] Desirable qualities of a marker will depend on why it is being measured. Markers used for screening need to have low costs, high sensitivity and specificity, high predictive values, and large likelihood ratios. On the other hand, when monitoring progression or response to therapy, sensitivity and specificity are not priorities since the resultant values are compared to previous

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[394] Ibid.

[395] Clerico et al., "New and Emerging Biomarkers of Heart Failure."

[396] Jennifer M. Aviles and Ronnier J. Aviles, "Advances in Cardiac Biomarkers," *Emergency Medicine Clinics of North America* 23, no. 4 (November 2005): 959–975.

results not to population cut-off values and for prognostic markers. In addition, cost is not usually as important since only those with the condition are tested. [397]

The need to detect subclinical damage early with economically feasible methods has increased the interest in using cardiac biomarkers in screening and monitoring. Biomarkers have become a proposed way to monitor cardiac function in cancer patients, which could be more cost-effective and less resource-intensive when compared to radiological procedures or biopsy. Additionally, biomarkers are typically more sensitive to small changes in cardiac function, and have improved diagnostic sensitivity and predictive values when compared to traditional methods. [398]

In heart failure, effective biomarkers should provide information regarding pathogenesis of heart failure, identify patients at risk, and assist in diagnosis and monitoring. Some biomarkers can also serve as therapeutic targets. [399] Each cardiac biomarker has characteristic release and clearance kinetics and these patterns can assist clinicians in diagnosis and monitoring. [400] There have been a number of markers that have been suggested for heart failure, including markers of inflammation (CRP), myocyte injury (cTnI) or stress (BNP), neuroendocrine hormones (endothelin), oxidative stress (oxidized LDL), and extra-cellular matrix remodeling (collagen pro-peptides).[401]

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[397] Vasan, "Biomarkers of Cardiovascular Disease."

[398] Alberto Dolci et al., "Biochemical Markers for Prediction of Chemotherapy-Induced Cardiotoxicity: Systematic Review of the Literature and Recommendations for Use," *American Journal of Clinical Pathology* 130, no. 5 (2008): 688–695.

[399] Braunwald, "Biomarkers in Heart Failure."

[400] Aviles and Aviles, "Advances in Cardiac Biomarkers."

[401] Braunwald, "Biomarkers in Heart Failure."

Examples of potential biomarkers in heart failure with their mechanisms are illustrated in Figure 3.3 and their references ranges are listed in Table 3.5. [402]

Figure 3.3 Processes and Corresponding Biomarkers for Detection in Cardiac Remodeling [403]
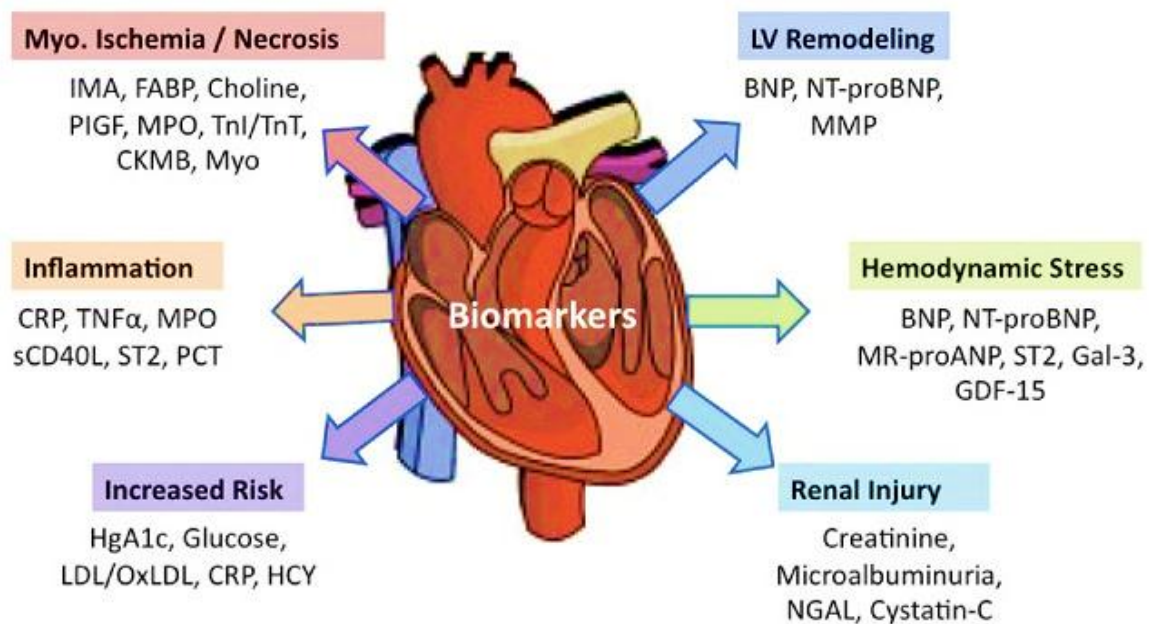
[402] Aurelia Macabasco-O'Connell and Pamela S. Miller, "Update on Heart Failure Management. Biomarkers for Heart Failure.," ed. Marla De Jong and Lynn Doering, *Progress in Cardiovascular Nursing* 21, no. 4 (October 2006): 215–218.

[403] Christopher Moriates and Alan Maisel, "The Utility of Biomarkers in Sorting Out the Complex Patient," *The American Journal of Medicine* 123, no. 5 (May 2010): 393–399.

Table 3.5 Reference Ranges for Biomarkers Used in Cardiac Dysfunction [404]

Biomarker	Reference Range Negative	Positive
BNP	< 100 pg/mL	≥ 100 pg/mL
NT-pro-BNP	< 125 pg/mL (< 75) < 450 pg/mL (≥75)	
CRP	< 0.8 mg/dL	
CRP High-Sensitivity	< 0.5 mg/dL	
Heart-Type FABP	< 6.2 µg/L	
IL-6	< 5 pg/mL	
Myeloperoxidase	< 539 pM	
Myosin Light Chain-1	< 2.5 µg/L	
Plasma Norepinephrine	112-658 pg/mL	
TNF-α	< 20 pg/mL	
TNF-receptor I	< 0.3 ng/mL	
TNF-receptor II	< 1.0 ng/mL	
Troponin T	< 0.10 ng/mL	
Troponin I	< 0.10 ng/mL	> 0.25 ng/mL

BNP: B-Type Natriuretic Peptide; NT-pro-BNP: N-Terminal – Pro-BNP; CRP: C - reactive protein; FABP: Fatty-Acid Binding-Protein; IL: Interleukin; TNF: Tumor Necrosis Factor

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[404] Macabasco-O'Connell and Miller, "Update on Heart Failure Management. Biomarkers for Heart Failure."

Markers of inflammation were shown in the Framingham heart study to identify asymptomatic patients that were at risk of the development of heart failure. [405] In animal models it has been shown that increased levels of TNF-α have resulted in LV dysfunction and examination of tissue from explanted hearts have shown higher myocyte mRNA expression of inflammatory markers such as TNF-α signifying local activation in patients with end-stage disease suggesting possibly utility as a marker. Unfortunately, markers for inflammation or oxidative stress these are not specific for heart failure which reduces their utility in routine clinical use. [406]

Elevated levels of markers for extracellular matrix (ECM) remodeling are associated with left ventricular dysfunction and could potentially serve as a target of therapy since degradation of the ECM has been shown to contribute to left ventricular remodeling. [407] However, since there have been over 15 markers of ECM degradation identified and it is not yet known which would provide the most useful information, these are not routinely used in clinical practice. [408]

Neurohormones are activated and circulate in response to a reduction in cardiac output. This compensation is effective in the short-term, however after long-term activation, this can worsen LV function. A number of neurohormones have been shown to predict hospitalizations and mortality in heart failure patients and can also serve as a therapeutic target. Additionally, markers of endothelial dysfunction have shown similar relationships with heart failure as elevated levels of makers for inflammation, oxidative stress or ECM degradation. Higher plasma levels of endothelin or endothelin-1

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[405] Braunwald, "Biomarkers in Heart Failure."

[406] Ibid.

[407] Eulalia Roig, "Usefulness of Neurohormonal Markers in the Diagnosis and Prognosis of Heart Failure," *Eur Heart J Suppl* 8, no. suppl_E (2006): E12–17.

[408] Braunwald, "Biomarkers in Heart Failure."

correspond to higher mortality in heart failure patients, although blocking the action of these substances does not confer improved outcomes. [409] Since neurohormones are not stable in plasma, measurement is difficult and although, neurohormones may serve as a predictor of outcomes, data are lacking that suggests these markers could be useful in screening, therefore routine use is limited. [410]

3.2.4.2   Troponins

Troponins (Tn) are proteins found in striated muscle. There are three subunits that regulate the calcium-dependent interaction between actin and myosin, which, in turn, forms complexes that regulate muscle contraction. (Figure 3.4) [411] The three subunits include the tropomycin binding subunit (T), the inhibitory subunit (I) and the calcium binding subunit (C). All three subunits are found in both cardiac and skeletal muscle, however, the calcium binding subunit is identical in both, therefore, it is not considered useful as a marker. [412] Currently available assays are able to detect levels of the cardiac specific isoforms of cTnT and cTnI and both are considered clinically equivalent in the detection of cardiac necrosis. [413]

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[409] Roig, "Usefulness of Neurohormonal Markers in the Diagnosis and Prognosis of Heart Failure."

[410] Braunwald, "Biomarkers in Heart Failure."

[411] P. J O'Brien, "Cardiac Troponin Is the Most Effective Translational Safety Biomarker for Myocardial Injury in Cardiotoxicity," *Toxicology* (2007).

[412] Jay L. Bock, "Evaluation of Cardiac Injury and Function," in *Henry's Clinical Diagnosis and Management by Laboratory Methods.*, ed. Richard McPherson and Matthew R. Pincus (Philadelphia: Saunders Elsevier, 2007), Chapter 18; John Sarko and Charles V Pollack, "Cardiac Troponins," *The Journal of Emergency Medicine* 23, no. 1 (July 2002): 57–65.

[413] Srinivasa Potluri et al., "Cardiac Troponin Levels in Heart Failure," *Cardiology in Review* 12, no. 1 (February 2004): 21–25.

Figure 3.4 Illustration of Troponin Mechanism in Myocyte Activation[414]
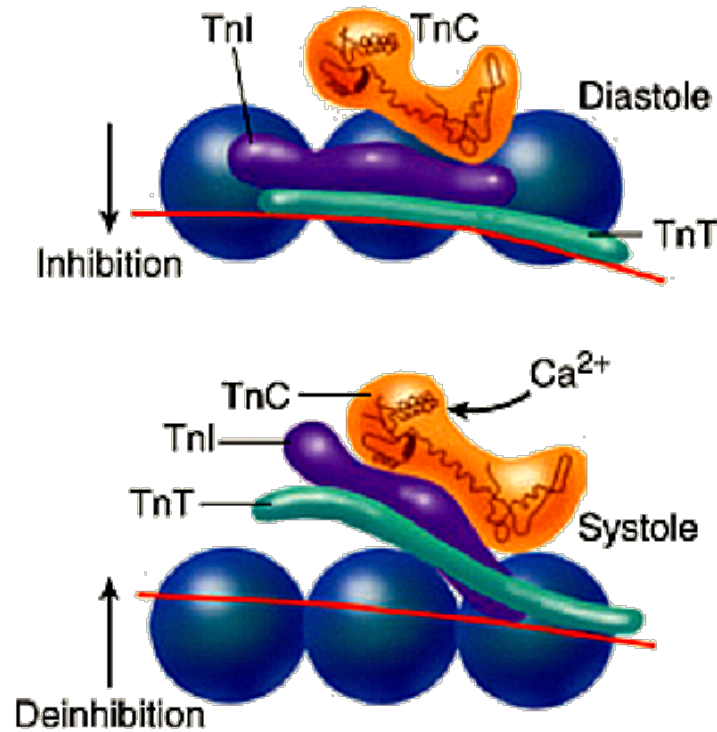
TnC: Calcium-Binding Subunit; TnI: Inhibitory Subunit;
TnT: Tropomycin Subunit

Traditionally, the cardiac specific troponins are used to detect damage during or after acute coronary syndromes (ACS) such as myocardial infarction (MI). Cardiac troponins have been used as a screening tool in this patient population, although, using the test in those with a low suspicion of ACS decreases the sensitivity and positive predictive value (PPV) to 47% and 19% respectively. [415] Troponins are able to diagnose, contribute to risk stratification and assist in designing appropriate care for patients with ischemic injury. They are now considered the "gold standard" biomarker in this

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[414] Bock, "Evaluation of Cardiac Injury and Function."

[415] Aviles and Aviles, "Advances in Cardiac Biomarkers."

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setting.[416] The cardiac specific troponins I and T are considered similar with respect to utility in diagnosis and prognosis as well as kinetics in acute coronary syndromes. [417] Typically, cardiac troponins are first detectable within two hours of the onset of symptoms, are considered maximally sensitive 8 - 12 hours later and peak 10 - 24 hours later, and are usually detectable for up to seven days but may persist for 14 days. [418]

In diagnosing ACS, the initial troponin has low sensitivity if drawn less than six hours after the onset of symptoms and needs to be redrawn in eight to twelve hours if negative. However, it can detect an MI up to two weeks after infarction and can be used for risk stratification and therapy selection. In addition, it has greater selectivity than prior markers (CK-MB) and can detect reperfusion. [419] There are other cardiac conditions besides ACS or MI that may show elevations in troponin measurements; these include myocarditis, pericarditis, CHF, LV dysfunction and cardiac trauma. There are non-cardiac conditions that also may show elevations in troponins (usually cTnT); these include renal disease (usually later stages), pulmonary embolism (PE), chronic muscle disease (muscular dystrophy), and sepsis. [420]

The serum half-life of cTnT is 120 minutes and it is highly sensitive for myocardial injury in the first 48 hours (with respect to the onset of symptoms). The level of cTnT can remain elevated for five to seven days, but can be detectable for up to 21

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[416] Braunwald, "Biomarkers in Heart Failure."

[417] Bock, "Evaluation of Cardiac Injury and Function."

[418] Ibid.; Fred F. Ferri, "Laboratory Values and Interpretation of Results," in *Practial Guide to the Care of the Medical Patient* (Philadelphia: Mosby/Elsevier, 2007), Chapter 15, http://www.mdconsult.com.ezproxy.lib.utexas.edu/das/book/body/196081449-5/985638051/1417/1347.html#4-u1.0-B978-0-323-04836-1..50018-6--cesec112_1854.

[419] Eugene Braunwald et al., "ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction: Executive Summary and Recommendations : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)," *Circulation* 102, no. 10 (September 5, 2000): 1193–1209.

[420] Bock, "Evaluation of Cardiac Injury and Function."

days. In patients with reduced renal function, cTnT more than cTnI can show false positives, therefore, cTnI is sensitive and considered more specific for myocardial injury; the level is elevated the first 8 hours, peaks in 24 hours and is detectable for up to seven days. Values for cTnI levels have a positive correlation with mortality as higher levels are suggestive of more extensive damage. [421] The normal range for cardiac troponins is < 0.04 ng/mL; a level within this range is considered a negative result and this is often reported as undetectable. The indeterminate range is from 0.05 to 0.49 ng/mL; levels within this range suggest additional testing if MI is in the differential diagnosis. Additionally, levels of Troponin I in this range are considered at risk for cardiac events in the near future. A level greater than 0.5 ng/mL suggests there is a strong probability of MI. [422]

3.2.4.2.1 Use of Troponins in Heart Failure

Since troponins can detect myocardial cell death, several recent investigations have shown increased interest in studying troponin levels in patients with heart failure. [423] There can be mild elevations in troponins seen in patients both with acute decompensated and chronic heart failure (without evidence of ischemia). [424] Additionally, it has been suggested that cardiac-specific troponins may provide additional information regarding the prediction of prognosis, mortality, and re-hospitalization in heart failure patients and could serve as a tool for risk stratification and as a potential therapeutic target. [425]

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[421] Ibid.; Ferri, "Laboratory Values and Interpretation of Results."

[422] Bock, "Evaluation of Cardiac Injury and Function"; Ferri, "Laboratory Values and Interpretation of Results."

[423] Sarko and Pollack, "Cardiac Troponins."

[424] Emile Missov, Charles Calzolari, and Bernard Pau, "Circulating Cardiac Troponin I in Severe Congestive Heart Failure," *Circulation* 96, no. 9 (November 4, 1997): 2953–2958.

[425] Potluri et al., "Cardiac Troponin Levels in Heart Failure."

In a recent retrospective investigation by Peacock and colleagues utilizing ADHERE data (Acute Decompensated Heart Failure National Registry), the investigators examined patients who were hospitalized for acute decompensated heart failure who had troponins measured on admission. The sample included 84,872 patients over a four-year period (2001 - 2004). It was found that patients with a positive troponin test for either cTnI or cTnT (n = 4,240), had significantly higher in-hospital mortality (8% vs. 2.7%, $p < 0.001$). The adjusted odds-ratio for death in patients with a positive troponin result was 2.55 (2.24 to 2.89, $p < 0.001$) and when examined on a continuous scale, higher troponin levels were associated with higher mortality. Other notable differences were the positive troponin group was significantly more likely to receive inotropes (18% vs. 9%, p < 0.001) and vasodilators (28% vs. 18%, p < 0.001) when compared to the negative troponin group and had a longer time to first diuretic dose (2.4 hrs. vs. 2.2 hrs. $p < 0.001$). [426]

The authors adjusted the odds-ratios for mortality for treatment with vasodilators or inotropes, the odds-ratios were and 1.84 (95% CI: 1.37 to 2.81) and 1.96 (95% CI: 1.43 to 2.36) respectively when comparing the troponin-positive versus the troponin-negative groups. When comparing treatment with inotropes versus vasodilators within each group, the adjusted odds-ratios for death were 4.44 (95% CI: 2.90 to 6.81) and 4.54 (95% CI: 3.75 to 5.49) for the positive and negative groups respectively. These authors do propose utility for troponins in this patient population for outcome prediction, however, they also stipulate that their study is retrospective and lacks the ability to establish cause and effect. [427]

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[426] W. Frank Peacock et al., "Cardiac Troponin and Outcome in Acute Heart Failure," *N Engl J Med* 358, no. 20 (2008): 2117–2126.
[427] Ibid.

Two studies were conducted by Missov and colleagues. The earlier of the two studies sought to determine whether cTnI was elevated in later stage heart failure patients, this was later extended to cTnT measurement in heart failure patients from all NYHA classes. In the first study investigators sought to determine if troponin I was a sensitive and specific marker for heart failure in patients with advanced disease. The study population consisted of 115 patients, 35 heart failure patients in NYHA classes III or IV, 55 patients that were healthy blood donors and 25 patients with hematological malignancies (without evidence of cardiac disease) to serve as hospitalized controls. Measurements were assessed both with a high sensitivity and the standard assay that have a lower limit of detection of 3 pg/mL and an upper reference limit of 1 ng/mL respectively. The use of the higher sensitivity assay provided detectable results from the control patients, the mean for the entire control population (n = 80) was 25.4 ± 2.9 pg/mL (20.4 ± 3.2 for healthy controls and 36.5 ± 5.5 for hospital controls). The mean cTnI level for the heart failure group was 72.1 ± 15.8 pg/mL; this was found to be significantly higher than the pooled, healthy, and hospitalized control groups ($p < 0.01$). Additionally, the authors were not able to demonstrate a difference between ischemic and idiopathic dilated cardiomyopathies or between NYHA classes III or IV. [428]

However, when the standard assay was used, only one patient had a level that was greater than the 1 ng/ml upper reference limit. Eight heart failure patients did not register a detectable level and the remaining 26 had levels that were below the upper reference limit. The authors concluded that these results provide strong evidence that the number of patients with positive tests depend on the sensitivity of the assay. They also conclude more work needs to be done in a larger population that includes heart failure patients

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[428] Missov, Calzolari, and Pau, "Circulating Cardiac Troponin I in Severe Congestive Heart Failure."

from all functional classes and examination of the possible implications of targeting levels as therapeutic outcomes. [429]

A second study conducted by Missov and Mair that looked at troponin T levels in heart failure patients. In the troponin T study, 33 consecutive patients with what was considered stable heart failure were enrolled for evaluation, 10 patients (30%) were in NYHA classes I or II and 18 patients (55%) had heart failure resulting from an ischemic etiology. The control group (n = 47) included age and gender matched healthy blood donors. The assay used in the study was a second generation assay that utilized 1 ng/ml as the diagnostic upper reference limit. [430]

The measured cTnT was significantly higher in the study population (0.140 ± 0.439) versus the controls (0.0002 ± 0.001) (p = 0.0001). There was also a statistically significant difference in cTnT between patients stratified on heart failure severity. Patients in NYHA classes III or IV (0.163 ± 0.50) had a significantly higher cTnT than those in NYHA class I or II (0.007 ± 0.01) (p = 0.04). The authors state that the increase in cTnT parallels the disease severity and the decline of left ventricular function (R = - 0.41, p = 0.01).[431] The authors did not find a significant difference between patients with ischemic cardiomyopathy and those with idiopathic dilated cardiomyopathy. The authors concluded that these results suggest that cTnT would be a viable, low-cost option in screening asymptomatic patients. [432]

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[429] Ibid.

[430] Emil Missov and Johannes Mair, "A Novel Biochemical Approach to Congestive Heart Failure: Cardiac Troponin T," *American Heart Journal* 138, no. 1 (July 1999): 95–99.

[431] Ibid.

[432] Ibid.

In a more recent study by Latini and colleagues, the investigators also examined troponin T with both the standard assay and a high-sensitivity assay to determine if there was a relationship between the detected level and patient prognosis. The authors intended to confirm previous findings in smaller studies which indicated that elevated troponin levels can predict adverse outcomes in heart failure. At the time of publication, the high-sensitivity assay was not commercially available. [433]

The Valsartan® Heart Failure Trial (VAL-HeFT) population included 5,010 patients, all of which had a LVEF of < 40% and were currently receiving heart failure pharmacotherapy. Troponin measurements were assessed at baseline (n = 4,053) and at follow-up four months later (n = 3,474) using both assays. The lower limits of detection for the standard and higher sensitivity assays were 0.01 and 0.001 ng/mL respectively. [434]

Of the 4,053 patients with troponin measurements, 420 (10.4%) had detectable values with the standard assay (median 0.027 ng/mL) compared to 92% of patients with a detectable level using the high sensitivity assay (median 0.012 ng/mL). Patients with elevated levels were more likely to be male, non-white, diabetic, and older, have a lower ejection fraction, and be classified in NYHA class III or IV. They were more likely to be treated with digoxin and diuretics, but less likely to have been receiving beta-blockers at study entry. Those patients also had elevated levels of neurohormones associated with poor prognosis. Of those patients from the placebo arm of the trial, disease was considered stable if the patients had < 2 kg change in body weight, < 5% change in ejection fraction, and unchanged NYHA functional class. There were 670 patients that met these criteria. [435]

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[433] Roberto Latini et al., "Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients With Stable Chronic Heart Failure," *Circulation* 116, no. 11 (September 11, 2007): 1242–1249.
[434] Ibid.
[435] Ibid.

The two main outcomes of interest were all-cause mortality and hospitalizations. Of the original patients, overall mortality was 16.5% and 43.3% for patients without and with detectable cTnT levels respectively (p < 0.0001). Mortality was 7.8% and 35.6% for the lowest and highest quartile of high sensitivity cTnT respectively. There was a similar trend in heart failure-related hospitalizations. In a separate Cox Multivariate analysis where cTnT was dichotomous (detectable vs. undetectable), the authors reported that detectable levels had the strongest association with all-cause mortality, reporting a hazard ratio of 2.08 (95% CI: 1.72 to 2.52). In a model substituting high sensitivity troponins, detectable levels were also the strongest predictor of mortality. In the model predicting hospitalizations, the standard and high sensitivity assays ranked sixth and seventh respectively. The authors then explored using both troponins and BNP as predictors. The VAL-HeFT data demonstrated a moderate correlation between the higher sensitivity assay and BNP (r = 0.441 p < 0.0001). In a prediction model, each predictor was added separately then together. BNP, and both high sensitivity and standard troponins, all were statistically significant predictors for both mortality (p < 0.001) and hospitalizations (p = 0.025). [436]

The authors concluded that troponin values which would be considered irrelevant clinically in the context of acute coronary syndromes appeared to be a valuable outcome prediction measure in stable heart failure patients. The addition of troponin, specifically the high sensitivity assay, adds to prognostic information and risk stratification for patients with stable heart failure. The authors also maintained that serial measurements can be clinically relevant and suggested that future studies focus on two or more markers as it appears BNP and troponins contributed unique information to the clinical picture. [437]

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[436] Ibid.

[437] Ibid.

3.2.4.2.2   Troponins in Cardiotoxicity

To date, there have been a number of studies that examined the use of troponins to monitor cardiac function in cancer patients with a total of approximately 1,500 patients. The bulk of the evidence provided in favor of the use of troponins, are four studies that are from the same group of investigators. In two of those studies, troponins were measured using an assay that is no longer commercially available (Dade Stratus II). Patients on cardiotoxic chemotherapy with positive troponins ranged from 30% to 38%, therefore the authors concluded that troponins were able to detect some level of myocardial injury in about one-third of patients receiving cardiotoxic chemotherapy.[438]; Cardinale et al 2002)

In the first of four studies, cTnI measurement was essentially identical for each protocol, values were evaluated immediately before, immediately after, and at 12, 24, 36, and 72 hours after receiving the drug (i.e., each patient had six measures per infusion), and only the highest values were considered. Patients were followed for ten months to determine if cardiotoxicity developed. All patients had values within normal limits at baseline and at each subsequent measurement (i.e., each measure would be considered negative using threshold criteria for ACS). [439]

Patients were classified as positive if levels were detectable, this occurred in 65 patients (32%), 59 (53%) of these patients had detectable levels immediately following drug administration, 10 (9%) at 12H, 21 (19%) at 24H, 8 (7%) at 36H, and 14 (12%) at 72H. Of those with detectable troponins, 19 (29%) had a measured LVEF < 50% at any time during follow-up compared to zero in the other group (p < 0.001). Three patients

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[438] D. Cardinale et al., "Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-dose Chemotherapy," *Circulation* 109, no. 22 (2004): 2749.
[439] Ibid.

developed symptoms of heart failure, all of which had detectable troponin levels, as well as a positive CK-MB and LVEF < 30% at the last evaluation prior to symptom onset. The maximal percentage change from baseline of end-systolic (ESV) and end-diastolic volumes (EDV) were calculated and found to be significant for both groups. The authors however, state that the changes were greater in the troponin-positive group. Additionally, the authors found that there was a significant relationship between the maximum troponin value and maximum LVEF reduction (r = - 0.87, p < 0.0001). Therefore, they concluded that positive troponin measurements could serve as a prediction tool for future systolic dysfunction. [440]

In a 2002 study these same investigators conducted essentially the same study with a longer follow-up (14 months instead of 10), except this study population was entirely breast cancer patients (n = 211). Patients were treated with one of four different regimens, two of which were anthracycline-based (n = 136), and all of the patients who received non-anthracycline regimens in this study had received anthracyclines in the neo-adjuvant setting. This study used the same assay, identical limits of detection for positive values and measurements were taken at the same times relative to drug dosing. [441]

Ten (4.7%) patients developed symptoms of heart failure during follow-up (LVEF range from 30 - 45%), three of which developed overt heart failure (LVEF < 30%), cTnI was within normal limits (WNL) at baseline and for each of the subsequent measures for all patients. A detectable value was reported in 33% of patients (n = 70) and in 120 cycles (19%) of chemotherapy. Patients with detectable levels were then categorized based on maximal troponin as either positive (≥ 0.05 ng/mL) or negative (< 0.5 ng/mL). In the

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[440] Ibid.

[441] D. Cardinale et al., "Myocardial Injury Revealed by Plasma Troponin I in Breast Cancer Treated with High-dose Chemotherapy," *Annals of Oncology* 13, no. 5 (2002): 710.

troponin-positive group, 17/75 (23%) previously received anthracyclines. In the troponin-positive patients, LVEF decline was observed after one month of follow-up and continued over the duration of follow-up, whereas, the troponin-negative group did not have a significant decrease in LVEF. [442]

Similar to the previous study, these authors found a significant relationship between the maximal troponin value and the maximal LVEF decline over the follow-up period (r = - 0.9, p < 0.0001), and between the number of positive assays (for each patient) and LVEF decline (r = - 0.93, p < 0.0001). Of the ten symptomatic patients, all had multiple detectable levels ranging between five and seven positives per patient (of 18 measurements). Conclusions were similar to the prior study. [443]

The 2003 study had a similar protocol to the previous two studies; however, a different assay was utilized. The population included 179 patients with varying diagnoses; this included nine patients from a previous pilot study. Troponins were measured at the same times as previously described and were interpreted in a similar fashion. However, the 99th percentile was obtained from testing 99 healthy individuals and the threshold value was determined to be ≥ 0.08 μg/L. An ECHO measurement was conducted at baseline and at 1, 2, 3, 4, 7, and 12 months. [444]

Patients were categorized as per the previous study protocols. Patients with positive results (n = 57) had an average of 2.7 positives per patient, detectable levels were spread homogenously among collection times with the exception of the final measure at 72 hours, which resulted in fewer positives. There was a trend toward an increasing number of positive values with the number of cycles. Patients in the positive group were

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[442] Ibid.

[443] Ibid.

[444] Maria Teresa Sandri et al., "Minor Increases in Plasma Troponin I Predict Decreased Left Ventricular Ejection Fraction After High-Dose Chemotherapy," *Clin Chem* 49, no. 2 (February 1, 2003): 248–252.

more likely to have received anthracyclines in the past (72% vs. 45%, $p < 0.05$), groups were balanced on all other characteristics at baseline including LVEF. Patients with positive troponins had an average decrease in LVEF of 6.8% after one month of follow-up, which progressively worsened over the evaluation period (at 12 months, the mean decrease was 18.2%). [445]

In comparison, the negative group had a mean LVEF decrease of 1.5% at one month and 2.5% after 12 months, which was statistically significant at each interval. Conclusions for this study were similar to previous studies, that measurement of troponins could provide a reliable early marker for myocyte damage secondary to chemotherapy and potentially identify "at-risk" patients. Furthermore, they speculated that although there were twenty patients with elevated levels that did not experience decreases in LVEF, this might be explained this by the short follow up period. [446]

In 2004, the same authors conducted a study including 703 patients with various malignancy types, during this study, the investigators gathered troponin values at the same times surrounding each dose of the drug. However, they also obtained cTnI levels one month after the conclusion of therapy and this was considered the late or L-cTnI level. Patients were categorized as to whether they had detectable levels in early measurements only (TnI +/-), early and late   (TnI +/+), or neither (TnI -/-). Troponin values in 70% (n = 495) of patients were below the cutoff in both early and late measurements and were categorized as TnI -/- . Of the remaining, 145 (70%) had detectable troponins in the early phase only and were categorized as TnI +/- and 63 (30%) continued to have detectable levels in the late phase and were categorized as TnI +/+.   Of 111 patients that experienced cardiac events, there were significant

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[445] Ibid.

[446] Ibid.

differences found when comparing patients who had late detectable values and those without (p < 0.001) and comparing patients with early positives and those without (p < 0.001).[447]

Additionally, from these studies, the authors concluded that troponins are able to predict clinically significant dysfunction up to three months in advance and that an early increase in troponins can predict the degree and severity of dysfunction. It must be noted that the dysfunction was detected using ECHO or MUGA scanning. It was determined from these trials that a persistent increase in troponins up to one month after chemotherapy is associated with greater cardiac dysfunction and an increased risk of cardiac events within the first year of follow-up than patients with only a brief increase. The negative predictive value was reported as 99% for patients who continually have negative troponins. [448]

A limitation to the use of cardiac troponins in monitoring is that peak levels are not seen consistently or in predictable patterns around chemotherapy administration. In the above listed trials, there were six measures taken for each administration of drug and the highest was considered for analysis, therefore it may be necessary to obtain serial measurements to provide useful information. [449] Multiple blood draws may make this unattractive in routine outpatient clinical practice. The authors of these studies justify the use of troponins by concluding that although multiple measures may be necessary, the cost of the test is low and negative values would exclude those patients from further expensive radiological procedures. However, they do not mention or allude to costs that would be involved in bringing the patient back to the clinic several times after drug

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[447] Cardinale et al., "Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-dose Chemotherapy."
[448] Ibid.
[449] Ibid.

administration to obtain these values, and although, the authors conclude the cost is justified and the method is cost-effective, no analysis is presented to support this conclusion. [450]

3.2.4.3   Natriuretic Peptides

Natriuretic peptides levels could also be obtained from relatively non-invasive blood draws and could provide another attractive alternative to traditional monitoring with ECHO or MUGA. Natriuretic peptides are neuro-endocrine hormones whose function in heart failure is to assist in fluid regulation (increasing urine volume and sodium excretion). BNP levels are known to increase proportionally with an increase in fluid volume and ventricular dysfunction.[451] The mammalian natriuretic peptide system involves three different substances; those are ANP (atrial natriuretic peptide), BNP (b-type natriuretic peptide) and CNP (c-type natriuretic peptide). The three peptides share a 17 amino acid ring. [452]

ANP was the first of the three to be described in 1983. ANP is synthesized and released into the atrium and its secretion is stimulated by stretch. ANP can also be found in ventricular tissue in patients with left ventricular hypertrophy but is not found in healthy ventricular tissue. ANP has an extremely short half- life lasting only one to two minutes in plasma, making measurement difficult. Therefore, for clinical purposes, NT-

[450] Ibid.; Cardinale et al., "Myocardial Injury Revealed by Plasma Troponin I in Breast Cancer Treated with High-dose Chemotherapy"; Sandri et al., "Minor Increases in Plasma Troponin I Predict Decreased Left Ventricular Ejection Fraction After High-Dose Chemotherapy."

[451] Aviles and Aviles, "Advances in Cardiac Biomarkers."

[452] Abassi et al., "Implications of the Natriuretic Peptide System in the Pathogenesis of Heart Failure."

ANP is measured in lieu of ANP since it is released in equal amounts and is not degraded as quickly. [453]

B-type natriuretic peptide (BNP) was formerly known as brain natriuretic peptide. It was initially called brain natriuretic peptide because it was originally identified in porcine brain in 1988. It consists of 32 amino acids, found in highest concentration in the atria, but because of the larger size of the ventricles, it is released in greater amounts from the ventricles. Both ANP and BNP have similar hemodynamic effects, which include increasing urine output and sodium excretion, decreasing systemic vascular resistance and central venous pressure, increasing cardiac output and decreasing blood volume. These actions subsequently cause arterial and venous dilation leading to reduced blood pressure and ventricular preload and are the exact opposite effects of the renin-angiotensin-aldosterone system (RAAS). [454]

ANP and BNP also have important central and peripheral sympathomimetic effects which include blocking cardiac sympathetic nervous system activity- even when cardiac filling pressures fall. They both also inhibit the renin-angiotensin-aldosterone axis; ANP infusion directly blocks secretion of renin and aldosterone and further inhibits the stimulatory effect of angiotensin II on release of aldosterone. BNP has direct relaxing properties in the myocardium and might have anti-proliferative and anti-fibrotic effects in vascular tissues. CNP does not act as a circulating hormone; it acts locally in vasculature as a vasodilator and inhibitor of vascular proliferation. [455]

BNP gene expression is induced within one hour of overload, which is one quality that makes it a good clinical marker. Chronic overload causes levels to be constantly

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[453] Ibid.

[454] James A de Lemos, Darren K McGuire, and Mark H Drazner, "B-type Natriuretic Peptide in Cardiovascular Disease," *The Lancet* 362, no. 9380 (July 26, 2003): 316–322.

[455] Ibid.

increased. It is secreted by both ventricles of the heart in response to stretching of the myocytes, and has a half-life of 20 minutes. [456] BNP is secreted with an N-Terminal fragment called NT-pro-BNP which is biologically inactive but has a longer half-life of one to two hours. Both have uses in screening and diagnosis and are also useful in determining prognosis, as those with higher levels experience worse outcomes. Both BNP and NT-pro-BNP are measured in pg/mL in U.S. assays.[457] Figure 3.5 illustrates the mechanism by which natriuretic peptides participate in fluid regulation. [458]

[456] Aviles and Aviles, "Advances in Cardiac Biomarkers."

[457] Abassi et al., "Implications of the Natriuretic Peptide System in the Pathogenesis of Heart Failure."

[458] Aviles and Aviles, "Advances in Cardiac Biomarkers."

Figure 3.5 Mechanisms and Role of Natriuretic Peptides in Heart Failure[459]
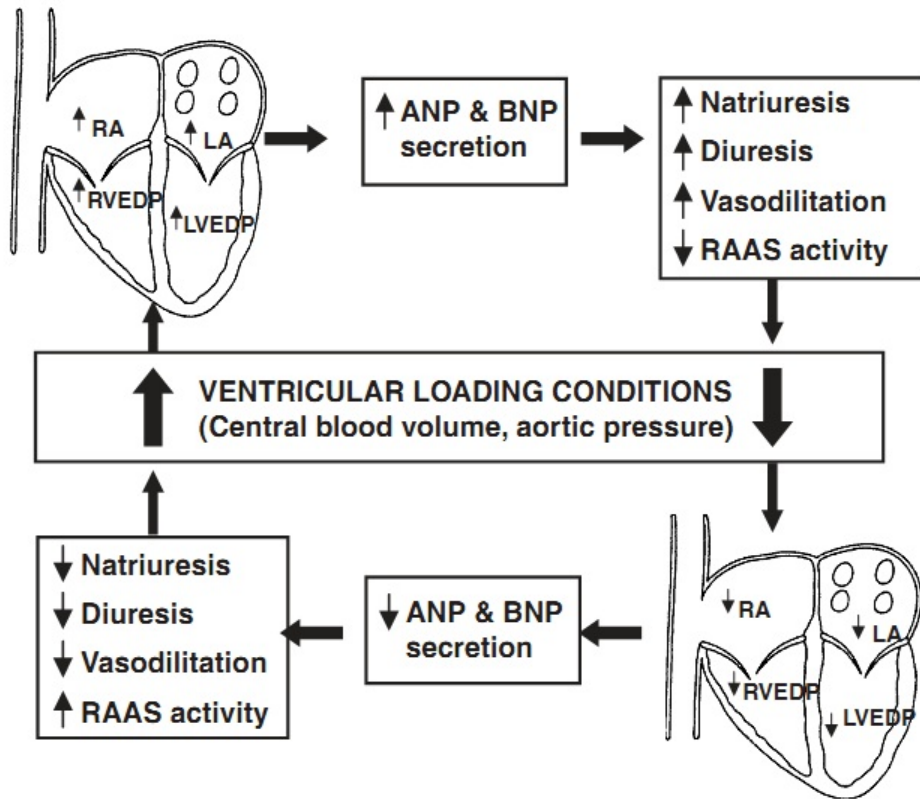
The stimulus for release for both ANP and BNP is myocyte stretch and both are synthesized as precursors and undergo intracellular modification to prohormones. ANP is sequestered in atrial storage granules and cleaved into a 98 amino acid (AA) N-terminal fragment. The 28 AA active hormones are released into the circulation and regulation occurs at the level of release from storage. BNP regulation takes place at the level of gene expression. BNP is synthesized in bursts and released from ventricular

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[459] Ibid.

myocytes as a 76 AA N-terminal fragment and a 32 AA active hormone. The expression of BNP can increase very rapidly in response to stimulus. In addition to primary regulation via myocyte stretch, synthesis can by augmented by tachycardia, glucocorticoids, thyroid hormones and vasoactive peptides such as endothelin-1 and angiotensin II independent of the hemodynamic effects of these factors. [460]

A third natriuretic peptide, CNP, was also found in porcine brain in 1990 and it was thought to be mainly a regulator, with actions primarily in the brain. CNP, however, also resides in vessels and can cause vasorelaxation of vascular smooth muscle. The plasma concentrations of CNP are extremely low and cause minimal diuresis and natriuresis. Most of the biological effects of all three natriuretic peptides occur via a second messenger system via guanosine monophosphate. There are three receptors identified which are NPR-A, NPR-B and NPR–C. NPR-C is a clearance receptor for ANP and BNP, the lower affinity of the NPR-C for BNP gives it a longer plasma half-life and thus, greater utility as a marker. [461]

BNP and NT-pro-BNP are well established markers for left ventricular dysfunction but are still seeing resistance to their routine use. Since it has been known since the 1950's that the heart was an endocrine organ, increased levels of such vasoconstrictors neurohormonal factors such as norepinephrine, renin, and enodthelin-1 have been found to be significant prognostic predictors in heart failure. Antagonizing these same neurohormonal factors has led to improvements in cardiac function. However, monitoring these factors is impractical because of instability, difficult assay characteristics with wide ranges and overlapping values, thus making natriuretic peptides

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[460] de Lemos, McGuire, and Drazner, "B-type Natriuretic Peptide in Cardiovascular Disease."
[461] Ibid.

better candidates for monitoring.[462] In a recent review, the authors suggest clinical trials should include rather than exclude patients that have cardiac risk factors in order to study new methods of monitoring and treatment. [463]

3.2.4.3.1 Available Assays

BNP can be measured using either traditional laboratory techniques or a bedside assay that has recently become available. The Triage® BNP test, according to the manufacturer Biosite®, is the only point of care assay available that is a CLIA waived blood test for BNP. The assay needs to be used with the Triage® meter. The Triage® BNP test is a fluorescent immunoassay that quantitatively measures BNP in whole blood or plasma using only EDTA as the anticoagulant.[464] Samples collected are stable for four hours. The test kit must be refrigerated and once opened, is stable at room temperature for 14 days. (http://www.alere.com/EN_US/index.jsp) The assay can detect values between 5 pg/mL and 1,300 pg/mL; however, the actual value can potentially be up to 3500 pg/mL.[465] The accepted upper limit of normal for BNP is 100 pg/mL. The Triage® BNP test gives results in 15 minutes, with a specificity of 98% and > 98% negative-predictive value with a cut-off of 100 pg/mL.[466] This study used the 2002 cost of the test kit for analysis, which was $26.

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[462] A. Maisel, "B-Type Natriuretic Peptide Levels: Diagnostic and Prognostic in Congestive Heart Failure: What's Next?," *Circulation* 105, no. 20 (2002): 2328–2331.

[463] Bird and Swain, "Cardiac Toxicity in Breast Cancer Survivors."

[464] Biosite/Inverness Medical, "Biosite® Inc. Web Site -- Triage® BNP Test," *Biosite*, n.d., http://www.biosite.com/products/bnp.aspx.

[465] W F. Peacock, "The B-type Natriuretic Peptide Assay: a Rapid Test for Heart Failure.," *Cleveland Clinic Journal of Medicine* 69, no. 3 (March 2002): 243–251; ibid.

[466] Peacock, "The B-type Natriuretic Peptide Assay: a Rapid Test for Heart Failure."; S Wieczorek, "A Rapid B-type Natriuretic Peptide Assay Accurately Diagnoses Left Ventricular Dysfunction and Heart Failure: A Multicenter Evaluation," *American Heart Journal* 144, no. 5 (November 2002): 834–839.

To be useful as biomarkers, peptides must be able to be measured rapidly and accurately at a reasonable cost, add diagnostic or prognostic information and help guide patient management. BNP and NT-pro-BNP fit most of these criteria in patients with heart failure, both BNP and NT-pro-BNP provide similar information and assays are available for both. [467] Candidates for assay use would be patients who present to an acute care setting with signs and/or symptoms suggestive of heart failure but in whom a diagnosis is in question. The assay can assist in distinguishing heart failure from respiratory reasons for dyspnea or renal reasons for edema. [468]

While high BNP is specific to heart failure, it does not preclude the existence of other disease states creating a potential limitation for use. Other limitations may include that patients with chronic heart failure may test with persistently high BNP values - so in determining their clinical status - comparison to their baseline value may be necessary. [469] Additionally, there are several disorders corresponding to small or intermediate increases in BNP, including right ventricular dysfunction or left ventricular hypertrophy (LVH). This would have to be considered when using the assay as a screening tool. Normal values have yet to be established, although levels are known to be affected by age, gender, renal failure and medication use (such as diuretics and beta-blockers). These factors need to be considered before use.[470]

With a number of limitations, the assay still has utility in diagnosis, screening, risk stratification, monitoring and tailoring therapy. [471] A recent paper by Cowie and

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[467] Wieczorek, "A Rapid B-type Natriuretic Peptide Assay Accurately Diagnoses Left Ventricular Dysfunction and Heart Failure: A Multicenter Evaluation."

[468] Ibid.

[469] M Cowie, "Clinical Applications of B-type Natriuretic Peptide (BNP) Testing," *European Heart Journal* 24, no. 19 (2003): 1710–1718.

[470] Ibid.

[471] Ibid.

colleagues describes two available assays, the first is a point-of-care rapid fluorescence immunoassay for BNP, which provides results in about 15 minutes and produces results that appear to correlate well those from radioimmunoassay. The second assay is an electrochemiluminescent assay available for measuring NT-pro-BNP and this yields results in about 18 minutes. The reference ranges for both assays vary depending on the assay method and the nature of the control population. In general, values rise with age and are higher in women than in men for matched ages. The suggested normal range for BNP is 0.5 – 30 pg/mL (0.15 – 8.7 pmol/L) and for NT- pro-BNP is 68-112 pg/mL (8.2 – 13.3 pmol/L). The suggested cut-off point for detection of heart failure is 100 pg/mL in those patients older than 55. For NT-pro-BNP the cut-off points in Europe are gender-specific with a cut-off of 100 for men and 150 for women. The cut-off is 125 for both genders in the US. [472]

The authors concluded that BNP testing is most valuable to non-specialist physicians in the diagnosis of heart failure. In practice, the assay should be used as a rule-out test, but for cardiologists, the assay does prove useful for monitoring outcomes and tailoring existing therapy. These authors also suggest there may be value in monitoring BNP values in selecting patients for transplant. Additionally, ejection fractions were noted if assessed within twelve months of the physical exam. The protocol defined systolic dysfunction as ejection fraction (EF) ≤ 45% and diastolic dysfunction as EF > 45%. Using these criteria, 231 patients had systolic dysfunction and 71 patients had diastolic dysfunction. [473]

A prospective multicenter study by Wieczorek and colleagues was designed to assess the use of a point-of-care assay to diagnose and evaluate heart failure severity

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[472] Ibid.
[473] Ibid.

using NYHA classification. The design categorized patients into three groups, the CHF group (n = 409), the control group (n = 473) and a second control group of patients with hypertension (n = 168). The CHF group included patients in all four functional classes of heart failure (the CHF group), the first control group included patients without heart failure or other cardiovascular disease, and the additional control group included patients with hypertension but without other cardiovascular disease. Samples were drawn from the hypertension group, when it was determined that their BNP levels were not significantly different than the control group, these groups were combined. Of the patients with heart failure, 28% were diagnosed with idiopathic heart failure, 43% were diagnosed with ischemic heart failure, 19% had other causes such as hypertension or alcoholism, and 10% had an unknown cause. [474]

Samples were drawn and examined in triplicate using the Triage® assay. Measurements were made using whole blood and plasma and there were no significant differences found. The findings for non-cardiac patients were inconsistent. The BNP levels were higher in women than in men and increased with age; this difference did not becoming significant until patients were over the age of 55. [475]

In the CHF groups, the circulating BNP increased with disease severity; however it was not possible to predict class because of the overlapping confidence intervals. The authors attributed this degree of overlap to the subjective nature of the classification system. The investigators also found a negative linear relationship between BNP and systolic ejection fraction. [476] The sensitivity and specificity of the assay was also tested in these patients. Using a cut-off of 100, the specificity was 97% and the sensitivity was

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[474] Wieczorek, "A Rapid B-type Natriuretic Peptide Assay Accurately Diagnoses Left Ventricular Dysfunction and Heart Failure: A Multicenter Evaluation."
[475] Ibid.
[476] Ibid.

82%. Using a ROC for each class plotted against BNP; BNP was able to separate normal patients from those in each class. Confidence intervals got wider as disease severity increased. The assay had the highest sensitivity and specificity when comparing the control to those patients in class four and had its lowest values when comparing the controls with the patients in class one. [477]

The authors concluded that BNP concentrations taken with bedside assay increased with CHF severity, differences were only seen between individuals with and without CHF. With a decision threshold equal to 100 pg/mL, this assay demonstrated 82% sensitivity and 99% specificity for distinguishing patients with CHF. These authors suggested that a lower threshold (such as 50 pg/mL), might also be useful as a negative predictive value. [478]

As previously discussed, there are several properties that would make any biological marker assay useful. BNP levels should be measured accurately and rapidly, and this is met by the currently available bedside assay where results are available in 15 to 30 minutes. Levels should not be changed by any property that does not change the state of cardiac compensation, which is the case of the Triage® assay; the results are not affected by any major class of cardiac drugs. Changing levels should be indicative of either de-compensation or improvement in function, which had been demonstrated in a number of studies. And, lastly, the assay should be able to be used to tailor therapy. [479] It has been shown that BNP levels correlate to elevated end diastolic pressure which in turn, correlates closely to the chief symptom of CHF which is dyspnea. The BNP levels

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[477] Ibid.

[478] Ibid.

[479] A Maisel, "B-type Natriuretic Peptide Levels: A Potential Novel 'white Count' for Congestive Heart Failure," *Journal of Cardiac Failure* 7, no. 2 (2001): 183–193.

correlate closely to NYHA classification, which would make it useful in tailoring therapy. [480]

A threshold of 100 pg/mL has been suggested to allow for the increased levels seen with advancing age and provides the ability to discriminate patients with CHF from patients without CHF. This level shows sensitivity from 82.4% for HF in general and increases to 99% for CHF in NYHA Class IV. Specificity exceeded 95% when comparing patients without HF with all patients with HF, and 93% in all subsets studied. It has been suggested by a number of researchers that a lower cutoff may be practical for screening large populations for LV dysfunction. [481] There is strong evidence suggesting that levels below 100 pg/mL have a strong negative predictive value for heart failure. Monitoring levels during acute decompensated states can be useful in gauging effects of short-term treatment. [482]

Maisel suggests that since heart failure affects 2% of the US population, is the fourth leading cause of adult hospitalizations, and is the most frequent cause of hospitalization in patients older than 65, finding a blood test to aid in diagnosis and management of heart failure clearly would have a favorable impact on the costs associated with the disease. Maisel cited direct costs of heart failure exceeding $38 billion, which accounts for over 5% of total health care costs. [483] When screening asymptomatic patients, it is important to consider the value used for a lower cut-off for negative predictive value. It has been suggested that a much lower value (such as 20

[480] Ibid.

[481] A Maisel, "B-type Natriuretic Peptide in the Diagnosis and Management of Congestive Heart Failure.," *Cardiology Clinics* 19, no. 4 (November 2001): 557–571.

[482] P. A McCullough et al., "B-type Natriuretic Peptides: a Diagnostic Breakthrough for Clinicians," *Reviews in Cardiovascular Medicine* 4, no. 2 (2003): 72–80.

[483] Maisel, "B-Type Natriuretic Peptide Levels: Diagnostic and Prognostic in Congestive Heart Failure: What's Next?".

pg/mL), be used when screening asymptomatic patients. [484] The half-life of BNP is about 20 minutes which suggests that it can accurately detect a change in pressure every two hours, whereas NT-pro-BNP has a half-life of about two hours which suggests that meaningful hemodynamic changes could be detected about every 12 hours. [485]

Like BNP, NT-pro-BNP is secreted from the ventricles as a result of increased stretch or tension and has been shown to correlate well with NYHA class. Concentration in plasma is about the same for BNP and NT-pro-BNP in healthy patients; however, for patients with heart failure, NT-pro-BNP can exceed BNP concentration by two to ten times, the mechanism of this difference is not yet know. It has been shown in animal studies that the half-life of NT-pro-BNP is much longer and this is often credited for the difference in concentrations.[486] The assay for the measurement of NT-pro-BNP can be conducted with several different analyzers, including the Roche Elecsys 1010[®], 2010[®] and E170[®]; all of which use the same detection technology (chemiluminescence) and analytical range (5 – 35,000 ng/L). [487]

A study to determine the precision and comparability of the assay was performed using samples with concentrations representing the entire analytical range, thus including healthy subjects and known heart failure patients (n = 1,205). Each subject had a full evaluation of risk factors, blood work including full biochemical profile (LFT's, lipid profile), and ECHO for measurement of LFEF. Patients were then categorized based on

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[484] McCullough et al., "B-type Natriuretic Peptides."

[485] Ibid.

[486] Christian Hall, "NT-ProBNP: The Mechanism Behind the Marker," *Journal of Cardiac Failure* 11, no. 5, Supplement 1 (June 2005): S81–S83; C Hall, "Essential Biochemistry and Physiology of (NT-pro)BNP," *European Journal of Heart Failure* 6, no. 3 (2004): 257–260.

[487] P Collinson, "Analytical Performance of the N Terminal Pro B Type Natriuretic Peptide (NT-proBNP) Assay on the Elecsys[TM] 1010 and 2010 Analysers," *European Journal of Heart Failure* 6, no. 3 (2004): 365–368.

risk factors and LVEF. Results from NT-pro-BNP were compared to both BNP and NT-pro-ANP. [488]

Of the study population, it was determined that 290 patients were without risk factors therefore patients represented the healthy population. The results from the healthy population demonstrated that NT-pro-BNP increases with age and with female gender. To determine the ability of the assay to detect LV dysfunction, patients were categorized on LVEF greater or less than 40%. The ROC curves for the 1) entire population, 2) low-risk patients and 3) high-risk patients were 0.913, 0.974, and 0.832 respectively. These authors concluded that the assay performed well and met criteria typically used to determine if an assay could be useful in practice. They also stated that further work was required but their preliminary data demonstrated that NT-pro-BNP was able to detect LV dysfunction. [489]

A study by Gustafsson and colleagues sought to determine the sensitivity and specificity of the NT-pro-BNP assay to detect LV systolic dysfunction in primary care patients and to predict death in these patients.[490] The sample included patients who were referred by their general practitioner to receive an ECHO because of suspected heart failure (n = 367). As a result of the ECHO, patients were categorized into three groups based on their ejection fraction, 1) > 40%, 2) > 30 but ≤ 40%, 3) ≤ 30%. The corresponding mean NT-pro-BNP levels were 136 pg/mL, 1,643 pg/mL, and 4,314 pg/mL respectively. The NT-pro-BNP levels were significantly higher in the LVEF ≤ 30% when compared to patients with LVEF > 30% (p < 0.0001), additionally, patients

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[488] Ibid.

[489] Ibid.

[490] Finn Gustafsson et al., "Diagnostic and Prognostic Performance of N-Terminal ProBNP in Primary Care Patients With Suspected Heart Failure," *Journal of Cardiac Failure* 11, no. 5, Supplement 1 (June 2005): S15–S20.

with LVEF ≤ 40% had significantly higher levels when compared to those with LVEF > 40% (p < 0.0001). The assay proved to be reasonably sensitive for patients with LVEF ≤ 40%; the sensitivities were 91% and 97% both with and without utilizing age-specific cut-off values respectively. While for patients with LVEF ≤ 30%, the test was 100% sensitive with or without adjustment of the cut-off value. [491]

While assays are available for both BNP and NT-pro-BNP, there are some distinct advantages of the BNP assay, including: it is available at the point-of-care, it is less influenced by age and renal function, it has a single approved value used for diagnosis, and it has a documented ability to discriminate between patients both with and without heart failure. [492] There are a number of positive points with the NT-pro-BNP assay as well. The NT-pro-BNP assay includes use on large laboratory platforms for economies of scale; its relationship to renal function has led some investigators to suggest that NT-pro-BNP may be an overall marker of cardio-renal function. However, a disadvantage for its use is that the cut-off for NT-pro-BNP is dependent on patient age. Both BNP and NT-pro-BNP have been shown to correlate well with heart failure severity (NYHA Class) so they can both contribute to objective assessment of patients, however, when compared head-to-head, BNP appears superior in identifying patients with left ventricular systolic dysfunction. [493]

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[491] Ibid.

[492] McCullough et al., "B-type Natriuretic Peptides."

[493] Ibid.

3.2.4.3.2 Natriuretic Peptides in Screening

In the PROBE-HF Study, investigators were attempting to determine the prevalence of asymptomatic heart failure in a population of patients at high risk and to evaluate the reliability of natriuretic peptide testing when compared to ECHO for diagnosis. There were 1,012 at-risk patients enrolled. Patients were considered at-risk if they had a diagnosis of type II diabetes or hypertension for which they had been receiving medication for at least the last six months- hypertensive patients had to be on at least two medications for six months. Systolic dysfunction was defined by ejection fraction ≤ 50% and categorized as mild (41 - 50%), moderate (31 - 40%), or severe (≤ 30%). The degree of diastolic dysfunction was determined via the ECHO parameters E/A ratio and deceleration time, and subsequently categorized as impaired relaxation, pseudo-normal, or restrictive pattern. Since the specificity for mild diastolic dysfunction is low, investigators pooled subjects with moderate-to-severe diastolic dysfunction and systolic dysfunction to create a subgroup for which greater specificity could be achieved. ECHO results were compared with those obtained via NT-pro-BNP testing to calculate the positive and negative predictive values for NT-pro-BNP and see if the test detected cases that were missed by ECHO. [494]

In the study population there were 633 patients (62.5%) with normal ECHO results. Of those with abnormal ECHO results (n = 379), 368 (36.4%), and eleven patients (1.1%) patients showed diastolic and systolic dysfunction, respectively. Patients with diastolic dysfunction (n = 368) was further classified into mild (n = 327, 32.4%) or moderate-to-severe (n = 41, 4%). The patients with moderate-to-severe diastolic

[494] Irene Betti et al., "The Role of N-terminal PRO-Brain Natriuretic Peptide and Echocardiography for Screening Asymptomatic Left Ventricular Dysfunction in a Population at High Risk for Heart Failure. The PROBE-HF Study," *Journal of Cardiac Failure* 15, no. 5 (June 2009): 377–384.

dysfunction were pooled with those with systolic dysfunction yielding a pooled subgroup of 52 patients. The patients with mild diastolic dysfunction were added to the group with normal ECHO results (n = 960). NT-pro-BNP levels were compared between the no dysfunction/mild dysfunction group and the moderate-to-severe systolic dysfunction group. NT-pro-BNP levels were significantly higher in patients with asymptomatic LV dysfunction than normal patients (258 pg/mL vs.74 pg/mL, $p < 0.001$).

In multivariate analysis, the likelihood of LV dysfunction was independently associated with (log) NT-pro-BNP levels ($p < 0.0001$). There was a significant difference in NT-pro-BNP levels between sub-groups of diastolic dysfunction. Patients with mild, moderate, and severe diastolic dysfunction had BNP levels of 146 ± 156 pg/mL, 317 ± 375 pg/mL, and 443 ± 416 pg/mL ($p < 0.001$) respectively. Additionally, the authors determined that a cut-off value of 125 pg/mL yielded the best sensitivity/specificity ratio, NPV and PPV for identifying patients with moderate-to-severe diastolic dysfunction (sensitivity 98%, specificity 80%, ROC AUC 0.93, NPV 99.8%, PPV 24%). These authors concluded that assessing NT-pro-BNP levels can lead to early exclusion of LV dysfunction in diabetic or hypertensive patients. Although tests such as an ECHO may provide more detailed information, NT-pro-BNP levels below the cut-off point of 125 pg/mL provided a high negative predictive value, whereas higher levels would warrant further evaluation with a test such as ECHO. Therefore, NT-pro-BNP levels could be used as an initial test to rule out LV dysfunction in high-risk patients. [495]

In a prospective study, Suzuki and colleagues sought to determine whether circulating BNP levels correlated with cardiac function while screening asymptomatic patients. All employees that were 55 or older working at the pharmaceutical company

[495] Ibid.

Shionogi were included unless taking anti-hypertensives. BNP was collected, and in those patients where BNP was > 18 pg/mL, a subsequent ECHO was done. During the ECHO, ejection fraction, fractional shortening, and mitral inflow E-wave to A-wave ratio were assessed as primary indices representing systolic and diastolic function. Additional ECHO parameters that were collected included left ventricular wall thickness of the intra ventricular septum and posterior wall, aortic root and left atrial dimensions and the left ventricular diastolic and systolic dimensions, in addition to heart rate. An ECHO was also conducted for age- and gender-matched controls from among the patients without elevated BNP measurements. [496]

The study population included 294 patients, and 49 patients had a BNP of > 18.4 pg/mL. The investigators found that BNP had significant correlations with multiple ECHO parameters. The authors concluded that the non-invasive nature of the test made it useful in screening the asymptomatic patient, with the addition of other tests such as an ECG and chest x-ray, to determine which patients might need more complex tests such as an ECHO. [497]

3.2.4.3.3   Natriuretic Peptides in Diagnosis

BNP can be useful to diagnose patients in the acute setting, where a quick and accurate diagnosis is needed, and misdiagnosis could lead to adverse outcomes. [498] Alternative tests such as ECG's, chest x-rays and ECHOs are accessible and have been used to detect heart failure; however, they can give results that are non-conclusive.

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[496] T Suzuki et al., "Screening for Cardiac Dysfunction in Asymptomatic Patients by Measuring B-type Natriuretic Peptide Levels," *Japanese Heart Journal* 41, no. 2 (March 2000): 205–214.
[497] Ibid.
[498] Maisel, "B-type Natriuretic Peptide in the Diagnosis and Management of Congestive Heart Failure."

ECHOs have additional issues including; the limited availability in the acute care setting, and the difficulty imaging patients with dyspnea or those who are obese. These downfalls decrease utility of the ECHO. [499]

A systematic review, conducted by Doust and colleagues, included 20 studies to determine the diagnostic accuracy of natriuretic peptides for heart failure. There were eight studies that measured BNP versus a criterion of LVEF of 40% or less, there were seven studies that compared BNP versus clinical criteria, and there were three studies that compared BNP versus NT-ANP. Inclusion criteria required that all studies that compared BNP and a reference standard have results that were reported such that a two by two table could be constructed. The authors excluded all case-control studies and those with overlapping populations (n = 6). [500]

Two reviewers extracted data and assessed the quality of each study. In the event of a disagreement; quality was assessed by a third reviewer. To allow for differences in cut-off points between studies, the reviewers calculated a diagnostic odds-ratio, and if there were more than one per study, the average was used. The diagnostic odds-ratio

(DOR) was calculated as: $\dfrac{\left(\frac{\text{Sensitivity}}{(1-\text{Sensitivity})}\right)}{\left(\frac{1-\text{Specificity}}{\text{Specificity}}\right)}$

Studies were grouped so that a DOR was calculated against each reference standard and if possible, positive and negative likelihood ratios were calculated where the studies had similar cut-off levels and reference standards. [501]

[499] Ibid.

[500] Jenny A. Doust et al., "A Systematic Review of the Diagnostic Accuracy of Natriuretic Peptides for Heart Failure," *Arch Intern Med* 164, no. 18 (October 11, 2004): 1978–1984.

[501] Ibid.

The investigators used an unweighted least squares regression to determine if the odds ratio was independent of the cut-off point. An unpaired two-tailed t-test was used to determine if the slope of the line was significantly different from zero, which would imply that the diagnostic accuracy of the test varied with the cut-off point. In those studies that compared BNP and ANP, the area under the curve for each study was pooled by an inverse variance method, diagnostic accuracy was assessed by taking the differences of the AUC's and dividing by the variances of the AUC. The overall quality of the included studies was considered good as judged by the six criteria determined by the authors. [502]

The authors of this paper concluded that BNP is accurate in the diagnosis of heart failure. Considering that the measurement of BNP is less expensive and more highly accessible than other choices, it is a viable alternative. One of the advantages is that the results can be obtained within about 20 minutes of the blood collection, which makes the test most useful in the ambulatory care setting to determine which patients need to be further evaluated. When using a cut-off level of 15 pmol/L (1 pg/mL = 0.29 pmol/L) the test achieves "high" sensitivity, and values below this can be excluded from diagnosis. [503]

A meta-analysis of the validity of BNP and NT-pro-BNP studies in the diagnosis of clinical heart failure, examined the effect of age and role in population screening for left ventricular systolic dysfunction. Like the previous study, authors summarized test performance in each study with a calculation of the diagnostic odds- ratio (DOR) which was pooled for BNP and NT-pro-BNP studies for purposes of comparing the two tests. Forty-seven studies were identified and 27 were included for analysis. Authors sought to determine: the accuracy of both BNP and NT-pro-BNP in diagnosing HF in symptomatic

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[502] Ibid.

[503] Ibid.

patients (inpatient or outpatient), test performance in studies where both assays are carried out on each study participant, effects of age or study setting on test performance, and the accuracy of tests to detect asymptomatic disease. [504]

The "Breathing not Properly" study included seven centers with a total of 1,666 patients who reported to emergency departments (ED) with a complaint of dyspnea and were subsequently screened for HF. There were 1,586 patients enrolled in the study, 48 patients had incomplete records and were therefore excluded. Other exclusion criteria consisted of advanced renal failure defined by calculated creatinine clearance (CrCl) of < 15 mL/min, acute myocardial infarction, and overt causes of dyspnea (i.e., trauma or injury). Data collection in the ED included demographics, clinical history and objective assessment of clinical signs which were gathered by research personnel present for entire stay in ED. Each participant was seen by a physician, and an ECG, chest x-ray and blood tests were categorized via a structured checklist. The research personnel then categorized the physicians' estimate of clinical probability using a visual analog scale. BNP was tested using the Triage® BNP assay. [505]

Thirty days after the visit, the charts without the estimate of CHF probability, were reviewed by two cardiologists who were not treating physicians. The Framingham risk scores and NHANES scores were also calculated. After all information was reviewed, if agreement was achieved then that case was categorized as either: group 1-dyspnea due to CHF, group 2 - history of CHF but dyspnea due to non-cardiac cause, or

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[504] B. Ewald et al., "Meta-analysis of B Type Natriuretic Peptide and N-terminal Pro B Natriuretic Peptide in the Diagnosis of Clinical Heart Failure and Population Screening for Left Ventricular Systolic Dysfunction," *Internal Medicine Journal* 38, no. 2 (2008): 101–113.

[505] P. A. McCullough, "B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis From Breathing Not Properly (BNP) Multinational Study," *Circulation* 106, no. 4 (2002): 416–422.

group 3 - dyspnea due to non-cardiac cause. To conduct a binary analysis, groups 2 and 3 were pooled. [506]

The cardiologists that were independent reviewers agreed 89.3% of the time, for the remainder of cases, additional information was requested, and if disagreement still existed, a decision was made by an end-points committee. Diagnosis was supported by Framingham (83%) and NHANES (86%) scores. [507] Diagnostic accuracy for BNP was 81.2%, with a sensitivity of 90%, and a specificity of 73%. The positive predictive value (PPV) was 75%; the negative predictive value (NPV) was 90%, and the positive likelihood ratio was 3.4. These researchers found that BNP adds about 10% to the accuracy of clinical judgment, and is especially useful for those patients in the intermediate category.[508]

In another analysis with the same participants (i.e. n = 1,586), Meisel and colleagues used the Triage® bedside assay for the diagnosis of HF in emergency department patients. The study had the same criteria for exclusion and diagnosis as described above. There were 452 patients who were diagnosed with CHF and returned for an ECHO within 30 days of their visit to the ER. Patients were categorized into two groups based on their LVED obtained via ECHO. Patients with LVEF > 45 were considered to have non-systolic dysfunction (n = 165) and patients with LVEF ≤ 45 (n = 287) were considered to have systolic dysfunction. The BNP was measured during the patients' initial visit as per above methods using the Triage® BNP assay.[509] Patients without a diagnosis of CHF had a significantly lower mean BNP (34 pg/mL) than patients

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[506] Ibid.

[507] Ibid.

[508] Ibid.

[509] Alan S Maisel et al., "Bedside B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure with Reduced or Preserved Ejection Fraction: Results from the Breathing Not Properly Multinational Study," *Journal of the American College of Cardiology* 41, no. 11 (June 4, 2003): 2010–2017.

with either non-systolic (vs. 413 pg/mL, p < 0.001) or systolic dysfunction (vs. 821 pg/mL, p < 0.001). Additionally, patients with non-systolic heart failure had a significantly lower BNP than patients with systolic dysfunction (413 vs. 821 pg/mL; p < 0.001). [510]

When comparing patients with non-systolic dysfunction with those without heart failure, the BNP assay with a cut-off point of 100 pg/mL had a sensitivity of 86% and a negative predictive value of 96%. The assay had an accuracy of 75% for detecting abnormal diastolic dysfunction and logistic regression revealed that BNP was the strongest predictor to differentiate systolic versus non-systolic dysfunction. [511] These authors had similar conclusions to the other "Breathing Not Properly" study in that BNP was useful in differentiating heart failure from non-heart failure patients and may additionally have utility in discriminating between systolic and non-systolic dysfunction, which usually cannot be differentiated using clinical indicators alone. [512]

In a prospective randomized controlled trial [BASEL] of 452 patients who presented with acute dyspnea, 225 patients were assessed using the BNP bedside assay and 227 patients were assessed using the "conventional diagnostic strategy". Time to discharge and total cost of treatment were the primary end points. Secondary end points were in-hospital and 30-day mortality. All patients underwent the same initial assessment; BNP was collected using the point of service assay in the study arm with a cut-off point of 100 pg/mL. If patients had a BNP < 100, it was decided that HF was an unlikely cause of dyspnea, those with BNP > 500 were treated with HF as the diagnosis and were given rapid therapy with diuretics, ACE inhibitors, nitroglycerin, and morphine,

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[510] Ibid.
[511] Ibid.
[512] Ibid.

while for those patients with levels between 100 – 500 pg/mL, further investigation was conducted. [513]

Time-to-discharge was defined as the difference between the time of presentation in the emergency department and the time of discharge; patients who died in the hospital were excluded from these calculations. To avoid differences resulting from a variety of third-party payers, hospital charges were standardized according to actual rates for patients with general insurance living is Basel, Switzerland. All endpoints were assessed in a blinded fashion by physicians who were not involved in patient care, but who had access to all medical records pertaining to each patient. [514]

The authors found that the use of the BNP assay reduced the need for hospitalization and an ICU stay. Additionally, the time to discharge was significantly shorter in the BNP group, which translated into significantly lower costs. Deaths in each group were not significantly different. Use of the BNP assay reduced the total cost of treatment by 26%. Authors concluded that the rapid measurement of BNP used with other clinical information in the emergency department, improves the care of patients with acute dyspnea and reduces costs and time to discharge. [515]

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[513] Christian Mueller et al., "Use of B-type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea," *The New England Journal of Medicine* 350, no. 7 (February 12, 2004): 647–654.
[514] Ibid.
[515] Ibid.

3.2.4.3.4 *Natriuretic Peptides in Cardiotoxicity*

It is well-documented that patients who receive cardiotoxic chemotherapy should be monitored closely; there are those who believe that this would ideally be with biomarkers such as troponins or BNP, especially when cardiac risk factors are present. [516] Biomarkers are useful, as they are specific for overload and stretch- the primary pathologic changes in heart failure. In a study of 111 patients at MD Anderson Cancer Center, a BNP level of > 150 pg/mL was 100% sensitive and 81% specific for a cardiac event, while BNP levels of > 200 pg/mL had an 88-fold increase in risk for cardiac event. LVEF was also monitored and was not predictive of these events. There is evidence that although symptoms are being reported by patients, these symptoms are not being evaluated or diagnosed appropriately by physicians. [517]

In a study by Lee and colleagues, which included 86 patients with hematologic malignancies receiving anthracycline chemotherapy, investigators sought to assess the correlation between BNP levels and cardiac complications. BNP and cTnI levels were measured in all patients prior to each chemotherapy cycle. The BNP lower limit of measurement was 5 pg/mL and the threshold value for normal was 100 pg/mL; the troponin lower limit of detection was zero and threshold value for normal was 0.2 ng/mL. For ECHO examination, the M-type, two-dimensional and Doppler ECHO were performed. [518]

During evaluation, 21 patients (24.4%) experienced some type of cardiac event. Cardiac events included heart failure (n = 15), heart failure with shock (n = 3),

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[516] Daniel J Lenihan, "Cardiotoxicity and Optimal Treatment," *Journal of Supportive Oncology* 6, no. 2 (February 2008): 77–79.

[517] Ibid.

[518] Ho Sup Lee et al., "Clinical Correlation Between Brain Natriutetic Peptide and Anthracyclin-induced Cardiac Toxicity," *Cancer Research and Treatment* 40, no. 3 (2008): 121.

arrhythmias (n = 2) and arrhythmia with heart failure (n = 1). Using univariate analysis, the authors found an association between the development of heart failure and several parameters including: maximum BNP level measured during chemotherapy (mean 305.8 pg/mL, p < 0.001), LVEF < 50% (mean 40.6%, p < 0.001), abnormal ECG (p < 0.001), and elevated cTnI (p = 0.002). Additionally, there appeared to be an association between increased age and the development of events, albeit, this also did not result in a statistically significant difference (p = 0.066). On multivariate analysis, elevated BNP (OR 1.017, 95% CI: 1.002-1.032, p = 0.029), elevated troponins (OR 52.231, 95% CI: 1.344 – 2,030.343, p = 0.034) and abnormal ECG (OR 26.035, 95% CI: 2.071 - 327.234, p = 0.012) were associated with cardiotoxicity. These authors concluded that elevated levels of BNP or cTnI may correlate with the development of cardiotoxicity; therefore, if abnormal results are found then preventive strategies must be employed to prevent additional damage. They also suggest that additional prospective studies should be conducted to understand the relationship between elevated BNP and development of cardiotoxicity. [519]

A small Japanese study evaluated the use of biochemical and myocardial markers of cardiotoxicity in a population of 27 patients. The population consisted of consecutive patients receiving anthracycline therapy for hematologic malignancies. Basal and post-chemotherapy levels of BNP, ANP, renin, aldosterone, angiotensin II, norepinephrine, epinephrine, CK-MB and myosin light chain along with ECHO measurements of ejection fraction and mitral valve inflow E/A ratio were measured (the frequency of

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[519] Ibid.

measurement was not explicitly stated). The cumulative dose of anthracycline received at study entry was 221.4 ± 53.7 mg/m^2. [520]

The investigators found that basal levels of BNP were elevated, and these levels increased significantly after patients received chemotherapy (31.1 ± 7.16 pg/mL to 58.1 ± 12.8 pg/mL; $p < 0.05$). The BNP reference value used for this study was < 19 pg/mL. The post-chemotherapy increase of ANP was also found to be statistically significant (14.1 ± 2.21 pg/mL to 29.2 ± 6.94 pg/mL, $p < 0.05$), although, the authors state that this is considered "non-diagnostic" as the increase was still below the reference value (< 43 pg/mL). There was also a rise in post-chemotherapy angiotensin II (24.5 ± 16.1 pg/mL) which was above the reference value (< 20 pg/mL); however, this rise was not found to be significant. The authors stated that the increases of BNP were transient in most patients lasting from three to seven days and returning to basal levels within two weeks. Three patients did experience persistently elevated BNP levels, two of which died from heart failure. The authors conclude that transient increases in BNP suggest a type of tolerance, and levels that are persistently elevated could be suggestive of a decompensation of this tolerance creating prognostic value for serial BNP levels. They also stated that the elevation of ANP and angiotensin II is suggestive of cardiac dysfunction, but further investigation is required to elucidate the utility of their serial measurement. The authors state that their findings suggest a possible role for the measurement of BNP after anthracycline administration; however, future studies with larger populations are required. [521]

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[520] T. Suzuki et al., "Elevated B-type Natriuretic Peptide Levels After Anthracycline Administration," *American Heart Journal* 136, no. 2 (1998): 362–363.

[521] Ibid.

Daugaard and colleagues conducted a study to evaluate potential utility of ANP and BNP measurements in the monitoring of patients for cardiotoxicity in order to assess whether ANP or BNP could replace obtaining LVEF measurements via MUGA scanning. Therefore, the reference standard used in this study was ejection fraction as measured by MUGA scans. There were 107 patients included in the study with a variety of cancer diagnoses and all patients had been treated with anthracyclines. There were a total of 204 measurements taken; there were simultaneous ejection fraction measurements and blood samples drawn. Pre-treatment values for either LVEF or natriuretic peptides were not obtained; the first measurement was taken when the patient had received 50% of the maximal cumulative dose. (450 mg/m^2) Therefore, some patients had several measures while others only had one. An ejection fraction of > 50% was considered normal; treatment was discontinued if patients had an ejection fraction < 50% or if their ejection fraction had decreased more than 10%. [522]

There were 48 patients in which multiple measures were taken, of which three (6%) developed heart failure (NYHA class II to IV), fifteen (31%) experienced a decrease in LVEF of > 10%, nine (19%) of those patients had a final measured LVEF < 50%. The authors found a relationship between low ejection fraction and elevated ANP and BNP in both the initial baseline measurements (n = 107) and all measurements (n = 208). They found statistically significant correlations between both ejection fraction and ANP (r = 0.78, p < 0.001) and ejection fraction and BNP (r = 0.76, p < 0.001) when ejection fractions are less than 50%, however, they did not find a similar relationship for ejection fractions > 50%. They also did not find associations between the change in ejection fraction and changes in natriuretic peptides levels during the duration of

[522] G. Daugaard et al., "Natriuretic Peptides in the Monitoring of Anthracycline Induced Reduction in Left Ventricular Ejection Fraction," *European Journal of Heart Failure* 7, no. 1 (2005): 87.

treatment. These authors therefore concluded that because they did not find a relationship between serial natriuretic peptide and ejection fraction measurements, natriuretic peptides cannot replace LVEF for cardiac evaluation of patients receiving anthracyclines. [523]

Kouloubinis and colleagues conducted a prospective study to determine the sensitivity of natriuretic peptide markers to evaluate cardiac function. The study had forty cancer patients divided into two nonrandomized treatment groups and two additional control groups. The treatment groups included patients with advanced disease that were to receive epirubicin and paclitaxel (Group A) and patients with early stage disease that were to receive mitoxantrone and docetaxel (Group B). The control groups consisted of women with heart failure (n = 13) in NYHA classes II, III or IV and healthy women (n = 20) without cancer or cardiac disease. Left ventricular ejection fraction, ECG, Pro-ANP and NT-pro-BNP were evaluated in all patients. Patients who had received chemotherapy with or without hormone therapy or radiotherapy within the prior six months were excluded. Significant cardiotoxicity was defined as LVEF decline of > 10% from baseline. LVEF was determined before chemotherapy and one week after completion, the control group with heart failure had LVEF values between 15 and 30%, and the healthy control group had LVEF values > 50. A twelve-lead ECG was obtained every three cycles for all patients; a QT interval > 440 ms was considered prolonged.[524]

Results showed a statistically significant increase in pro-ANP and NT-pro-BNP levels in group A (p = 0.0001), whereas the increase in group B was not significant (p = 0.43). There was no difference in the natriuretic peptide levels prior to treatment between

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[523] Ibid.

[524] A. Kouloubinis et al., "ProANP and NT-proBNP Levels to Prospectively Assess Cardiac Function in Breast Cancer Patients Treated with Cardiotoxic Chemotherapy," *International Journal of Cardiology* 122, no. 3 (2007): 195–201.

treatment groups and the healthy control group. However after treatment, both natriuretic peptide levels (pro-ANP and NT-pro-BNP) were significantly elevated compared to the healthy controls ($p = 0.0001$ and $p = 0.0002$), and none of the factors such as age, HER-2 status, grade, estrogen or progesterone status, or metastases were found to be significantly related to either pro-ANP or NT-pro-BNP. [525]

The LVEF was found to decrease significantly in the high-risk cardiotoxic regimen ($p = 0.0001$). The high-risk group had three patients experience a decrease in LVEF of $> 10\%$, and three experienced a decrease resulting in an LVEF < 50 (one patient common to both). There was a significant correlation found between the increase in both natriuretic peptides and the decrease in LVEF for Pro-ANP ($r = 0.8$, $p < 0.0001$) and NT-pro-BNP ($r = 0.7$, $p < 0.0001$). There were no significant correlations found for Group B. There were no significant ECG changes found in any group. In group A, 12 patients died from metastatic disease and two patients developed congestive heart failure.[526] These authors concluded that even at low cumulative doses of epirubicin, cardiac dysfunction can present as a serious side effect of therapy; pro-ANP and NT-pro BNP might be used as reliable markers in the detection of both early and late cardiac dysfunction. [527]

In a study to determine any possible relationship between NT-pro-BNP and acute post-anthracycline cardiotoxicity, Cil and colleagues enrolled 33 newly diagnosed patients with early disease. Any patients who had received previous treatment with chemotherapy, radiation or hormone therapy were excluded. Patients had an ECHO determination of LVEF, in addition to ECG and the measurements of NT-pro-BNP, troponin I, CK-MB and myoglobin prior to and after the conclusion of chemotherapy.

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[525] Ibid.

[526] Ibid.

[527] Ibid.

Patients were classified into either decreased or normal LVEF; those that had any decline in LVEF from first to last evaluation were classified into the "decreased LVEF" group. [528]

Prior to therapy, there were no differences between LVEF, blood pressure, heart rate, NT-pro-BNP, troponin I, CK-MB, myoglobin between the decreased and normal LVEF groups. However, after treatment, the patients in the "decreased LVEF" group had significantly higher NT-pro-BNP (p = 0.02) and lower LVEF (p < 0.001) than the patients in the normal LVEF group. There continued to be no differences in blood pressure, heart rate, troponin I, CK-MB and myoglobin between groups and no significant changes in ECG readings, symptoms, or physical indications of heart failure in either group. Additionally, there was no association found between NT-pro-BNP levels and hormone receptor status, disease grade, HER-2 status or number of breast cancer risk factors. [529] These authors concluded that although their study size was small, they did find an association between higher NT-pro-BNP levels and reduced LVEF. They suggested that this could potentially indicate early sub-clinical cardiotoxicity secondary to anthracycline administration and larger studies are needed to confirm these results. [530]

A retrospective analysis by Sandri and colleagues sought to determine if there was a predictive role for the measurement of NT-pro-BNP in patients receiving cardiotoxic chemotherapy. The study included 52 patients who received high dose chemotherapy and had cardiac evaluations (including ECHO) prior to therapy and at four and 12 months post therapy for aggressive malignancies. These same authors did a number of

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[528] T. Cil et al., "Use of N-Terminal Pro-Brain Natriuretic Peptide to Assess Left Ventricular Function After Adjuvant Doxorubicin Therapy in Early Breast Cancer Patients: A Prospective Series," *Clinical Drug Investigation* 29, no. 2 (2009): 131–137.

[529] Ibid.

[530] Ibid.

investigations using cardiac troponins in this population, and NT-pro-BNP was measured from stocked specimens. The measures were obtained at baseline, at the end of each infusion, and 12, 24, 36 and 72 hours after chemotherapy (times were determined as part of other protocols). [531]

Cut-off values used were those suggested by the manufacturer (153 ng/mL and 88 ng/mL, 334 ng/mL and 227 ng/mL for women and men $\leq$ 50 and > 50 years old respectively). After levels were determined at each time point, patients were then categorized into three groups based on the changes in NT-pro-BNP values. Group A (n = 17) consisted of patients whose NT-pro-BNP values rose after the infusion and continued to be elevated 72 hours later (i.e., those with persistently elevated levels), Group B (n = 19) had elevated values after 12 - 36 hours but trended back to baseline at 72 hours (i.e., transient increases only), and Group C (n = 16) had levels that decreased from baseline to 72 hours post infusion (i.e., no increases). There were nine patients (17.3%) that had values at baseline above the cut-off, three were in each group. There were no differences between the three groups with respect to gender, age, or malignancy type. [532]

At twelve months of follow-up, only Group A saw a significant decline in LVEF. The mean LVEF measurements for Group A obtained at baseline, four, and twelve months of 62.8%, 54.4% and 45.6%, respectively (p < 0.0001). There were no patients in Groups B or C that had an LVEF of < 55% after twelve months, whereas 59% of Group A patients met this criterion, four of which had overt signs of heart failure. These authors concluded that their results confirm previously reports that there is a relationship between elevated natriuretic peptides and cardiac dysfunction in patients receiving anthracycline

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[531] Maria T. Sandri et al., "N-Terminal Pro-B-Type Natriuretic Peptide After High-Dose Chemotherapy: A Marker Predictive of Cardiac Dysfunction?," *Clin Chem* 51, no. 8 (August 1, 2005): 1405–1410.
[532] Ibid.

therapy. Additionally, persistently elevated NT-pro-BNP is suggestive of some type of myocardial damage and levels may help to identify patients at increased risk. [533]

3.3 Comparisons of Monitoring Methods

In 2009, Troughton and Richards reviewed the use of the potential of integrating BNP, NT-pro-BNP, and ECHO measures to assess cardiac function and clinical status and to provide predictions regarding outcomes. The authors compared values of the natriuretic peptide assays with indices of cardiac function as measured by ECHO, both BNP and NT-pro-BNP correlate with dimensions, volumes, mass and pressure estimates of both ventricles, and are negatively correlated with LVEF. The strongest correlation was between BNP and LV diastolic wall stress; this was independent of ejection fraction, age, gender, and renal function. Both BNP and NT-pro-BNP had high negative predictive values (> 90%) for diastolic dysfunction when below threshold values of < 100 pg/mL for BNP and < 140 pg/mL for NT-pro-BNP. Additionally, in patients with normal ejection fractions, both are the strongest predictors of severe diastolic dysfunction when elevated levels are detected (i.e., BNP > 100 pg/mL and NT-pro-BNP > 600 pg/mL). [534]

When used in either the detection of diastolic dysfunction or in a screening setting (usually consists of patients with suspected dysfunction that have been referred for ECHO); BNP demonstrates a high sensitivity 85 - 90% when compared to ECHO. [535] In

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[533] Ibid.

[534] Richard W. Troughton and A. Mark Richards, "B-Type Natriuretic Peptides and Echocardiographic Measures of Cardiac Structure and Function," *JACC: Cardiovascular Imaging* 2, no. 2 (February 2009): 216–225.

[535] E. Lubien, "Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction: Comparison With Doppler Velocity Recordings," *Circulation* 105, no. 5 (February 2002): 595–601; Alan S. Maisel et al.,

screening studies, the prevalence of LV dysfunction is usually low (< 6%) and as the prevalence of dysfunction increases, so do both specificity and positive predictive value. Despite the low prevalence, negative predictive values remain high (93 - 99%) for natriuretic peptides that measure below threshold values. [536]

The Olmstead County group found that using age- and gender-adjusted cut-off values for diagnosis, both sensitivity and specificity range from 90 - 100% in detecting LV dysfunction in the general population. [537] The use of clinical presentation or tests such as ECG in conjunction with natriuretic peptide levels can improve positive predictive value and specificity, and use of an ECHO is usually recommended for a definitive diagnosis of heart failure when values are in the intermediate or "gray" range. [538]

Additionally, both BNP and NT-pro-BNP are the strongest two predictors of events and mortality in heart failure patients, and serial levels have been shown to be useful in the monitoring of chronic therapy, whereas serial ECHO measurements are not recommended. The authors concluded that BNP and NT-pro-BNP are useful in the screening and evaluation of patients with asymptomatic LV dysfunction; ECHO should be used to evaluate patients with levels in the intermediate or "gray" range to improve

"Utility of B-natriuretic Peptide as a Rapid, Point-of-care Test for Screening Patients Undergoing Echocardiography to Determine Left Ventricular Dysfunction," *American Heart Journal* 141, no. 3 (March 2001): 367–374.

[536] Lubien, "Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction: Comparison With Doppler Velocity Recordings"; Maisel et al., "Utility of B-natriuretic Peptide as a Rapid, Point-of-care Test for Screening Patients Undergoing Echocardiography to Determine Left Ventricular Dysfunction."

[537] Margaret M Redfield et al., "Plasma Brain Natriuretic Peptide to Detect Preclinical Ventricular Systolic or Diastolic Dysfunction: A Community-Based Study," *Circulation* 109, no. 25 (2004): 3176–3181.

[538] Troughton and Richards, "B-Type Natriuretic Peptides and Echocardiographic Measures of Cardiac Structure and Function."

accuracy and provide a more powerful prediction of risk of future cardiac events or mortality. [539]

In a study by Feola and colleagues, the authors prospectively examined relationships between LVEF changes seen via MUGA scanning with biochemical markers in breast cancer patients who had received anthracyclines (epirubicin). Enrolled patients (n = 53) were categorized into two groups at the conclusion of a two-year follow-up period. Group A (n = 13) included patients that experienced a cardiac event during surveillance, two of which developed symptomatic heart failure. Group B (n = 40) consisted of the patients who did not experience any cardiac changes during that time. Measurements were taken at baseline, one month (T1), one year (T2) and two years (T3) post-chemotherapy. Measurements included the following: a clinical assessment, troponin I, BNP, and radionuclide ventriculography. An event was defined as a decrease of LVEF of > 10% or overt HF. [540]

By T3, 13 patients (24.5%) had developed a cardiac event, two of which exhibited symptoms of heart failure, these patients comprised Group A while the remaining 40 patients (75.5%) who did not experience a cardiac event during follow-up comprised Group B. The investigators did find that the patients in Group A were older (p = 0.04), and differed in baseline, T1 and T2 BNP levels (p = 0.02), baseline heart rate (p = 0.001), and baseline hemoglobin levels (p = 0.007), although in multivariate analysis, the only parameter that showed a trend toward a relationship with T3 LVEF was baseline BNP (p = 0.07). Troponin measurements showed a release at T1 (p < 0.01) that disappeared at T2, this release was demonstrated in both groups and was not statistically different

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[539] Ibid.

[540] Mauro Feola et al., "Cardiotoxicity After Anthracycline Chemotherapy in Breast Carcinoma: Effects on Left Ventricular Ejection Fraction, Troponin I and Brain Natriuretic Peptide," *International Journal of Cardiology* (2009), http://linkinghub.elsevier.com/retrieve/pii/S0167527309015757.

(p = 0.04). These authors concluded that these results suggest that neurohormonal activation as measured by BNP levels could be a valuable tool to predict future LV dysfunction and further studies with larger samples are advised. [541]

3.4 Economic Implications

3.4.1 ECONOMIC IMPLICATIONS IN HEART FAILURE

BNP would be expected to have a favorable impact on costs as a non-invasive point-of-care tool for screening patients that present with dyspnea and those patients for whom a referral for an ECHO may be considered. It has been shown to correlate well with left ventricular pressure, the amount of dyspnea, and the state of neurohormonal modulation[542]. The assay has a reliable negative predictive value; therefore, those without left ventricular dysfunction have a low probability of being misdiagnosed. [543] Acute symptoms of heart failure overlap many other conditions such as COPD. This necessitates rapid diagnosis since giving sympathomimetic drugs that are routine for COPD, would be harmful to patients with CHF. [544]

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[541] Ibid.

[542] Maisel, "B-type Natriuretic Peptide Levels: A Potential Novel 'white Count' for Congestive Heart Failure."

[543] McCullough et al., "B-type Natriuretic Peptides."

[544] Ibid.

Studies have shown that more rapid and accurate diagnosis of heart failure results in a decrease in hospitalizations, time to discharge and initial treatment cost. [545] One investigation used data from a study that was described previously in this chapter to estimate costs associated with BNP testing. They assumed the cost of a BNP test was $47, and used hospital charges. Because of the short follow up period, neither adjustment nor discounting was conducted. [546]

Follow-up was completed in 451 of the patients initially enrolled. Data regarding hospital charges (treatment costs) were equally available in both the BNP and control groups. During the initial presentation to the emergency department, the use of BNP levels reduced the need for hospitalizations and ICU care. BNP levels also reduced the need for ventilator support and the number of ECHO procedures performed during initial presentation. At 180 days, all-cause mortality was 20% in the BNP group and 23% in the control group which was found to be not significant. Patients assigned to the BNP group spent significantly fewer days in the hospital than the control group, reducing total treatment costs when compared to the control group (p = 0.004). The reduction in total treatment costs was mainly driven by the reduction of days spent in the hospital. [547]

These authors found that BNP testing was cost-effective and significantly reduced treatment costs; $5,410 vs. $7,264, (p = 0.006) for initial treatment, and $7,930 vs. $10,503 (p = 0.004) for BNP and control groups respectively. Sensitivity analyses

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[545] Alan S Maisel et al., "Rapid Measurement of B-type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure," *The New England Journal of Medicine* 347, no. 3 (July 18, 2002): 161–167; McCullough, "B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis From Breathing Not Properly (BNP) Multinational Study"; Mueller et al., "Use of B-type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea."

[546] Christian Mueller et al., "Cost-effectiveness of B-type Natriuretic Peptide Testing in Patients with Acute Dyspnea.," *Archives Of Internal Medicine* 166, no. 10 (May 22, 2006): 1081–1087.

[547] Ibid.

indicated that these results were robust to changes in all variables except re-hospitalization with BNP guidance. [548]

A prospective screening study by Heidenreich and colleagues was designed to assess if BNP population screening for LV systolic dysfunction would be cost-effective. There were four different screening strategies examined. First, BNP testing; if result abnormal, the patient would get an ECHO. Patients whose ECHO showed an EF < 40 were given an ACE inhibitor to prevent the development of HF. The second strategy used only BNP levels to determine which patients would be treated. The third strategy sent all patients for an ECHO. The fourth strategy was no screening. Each test had one of four results, true positive, true negative, false positive or false negative. [549]

A model was developed to determine the lifetime health and economic outcomes for several hypothetical cohorts. The first was of 60 year-old patients with depressed EF (< 40) but without history who were given treatment with ACE inhibitors. The second cohort included patients with depressed EF but without history and no treatment until HF developed. The third included patients without depressed EF. Each month, patients with a low EF and without a history of HF can remain asymptomatic, develop HF or die. For those patients developing HF, it was assumed that 33% would be hospitalized during the initial episode of HF. Once patients developed HF, they could remain stable, be hospitalized or die during each time period. The model followed patients until all had died. The study used a BNP cost of $30. [550]

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[548] Ibid.

[549] Paul A Heidenreich et al., "Cost-effectiveness of Screening with B-type Natriuretic Peptide to Identify Patients with Reduced Left Ventricular Ejection Fraction," *Journal of the American College of Cardiology* 43, no. 6 (2004): 1019–1026.

[550] Ibid.

The authors found that in 1,000 men, using the strategy of BNP followed by ECHO, there was improved outcome at a cost of $22,300 per quality-adjusted life-year (QALY) gained when compared to no screening. If quality-of-life is ignored, then BNP screening costs $23,500 per life-year gained when compared to no screening. Screening with ECHO alone costs more than $100,000 per QALY gained and screening with BNP alone was more expensive and led to worse outcomes. For women, the screening with BNP followed by ECHO was $77,700 per QALY, while screening with BNP alone or ECHO alone were both dominated by the BNP-ECHO combination. The authors concluded that BNP followed by ECHO was cost-effective in men and possibly for women aged 60 and up. [551]

In a model constructed by Zomer and colleagues, the authors evaluated the cost-effectiveness of screening asymptomatic high-risk patients using BNP levels. The model included subsequent treatment with enalapril for those patients identified with left-ventricular dysfunction. There were three health states considered: alive with asymptomatic LV dysfunction, alive with symptomatic heart failure and dead, probability estimates for each state, hospitalizations and mortality were obtained from the SOLVD trial. Costs were obtained from a published paper by Liao and colleagues. [552] Calculations were conducted using three estimates of underlying prevalence of asymptomatic LV dysfunction (10, 20 and 30%) with a five-year time horizon. At five years, these authors found that for BNP screening strategies, the costs per LY gained were $40,306, $28,727 and $25,414 for prevalence estimates of 10, 20 and 30% respectively. These amounts decreased each subsequent year. These authors concluded

[551] Ibid.

[552] Lawrence Liao et al., "Long-term Costs and Resource Use in Elderly Participants with Congestive Heart Failure in the Cardiovascular Health Study," *American Heart Journal* 153, no. 2 (February 2007): 245–252.

that screening with BNP and subsequent treatment with enalapril was a cost-effective strategy for decreasing heart failure related morbidity and mortality. [553]

An investigation by Galasko and colleagues sought to determine the most cost-effective strategy to screen for LV systolic dysfunction. The methods under comparison included traditional ECHO, hand-held ECHO, ECG and NT-pro-BNP; the traditional ECHO was considered the gold-standard method of evaluation for this study. Subjects initially either had one or a combination of tests utilizing one of eight strategies under study. There were a total of 1,205 subjects, comprised of 734 from the general population, and 471 known to be at high risk. Upon assessment of the 734 from the general population, 290 had risk factors and were placed in the high-risk group (added to 471 high-risk patients for a total n = 762). This left 444 patients from the general population who were without risk factors and therefore classified as low-risk. All patients completed a questionnaire, received an ECHO and ECG, and had their blood drawn for a NT-pro-BNP level. Investigators then used a series of eight strategies for the detection of LVSD. [554]

Results indicated that screening low-risk patients was always the least cost-effective regardless of the strategy employed when comparing to the general population and high-risk groups. Strategy 7, which used a detection strategy of ECG first, then hand-held ECHO, then traditional ECHO had the lowest cost per detected case in all risk groups. This strategy had costs of €12,960, €884 and €649 per detected case for low-

[553] Ella Zomer, Danny Liew, and Bert Boffa, "Cost-effectiveness of Screening BNP-levels in Patients At-risk of Asymptomatic Left Ventricular Dysfunction," *Heart, Lung and Circulation* 17, no. Supplement 1 (2008): S53.

[554] Gavin I. W Galasko et al., "What Is the Most Cost-effective Strategy to Screen for Left Ventricular Systolic Dysfunction: Natriuretic Peptides, the Electrocardiogram, Hand-held Echocardiography, Traditional Echocardiography, or Their Combination?," *European Heart Journal* 27, no. 2 (2006): 193–200.

risk, general population, and high-risk groups respectively. Screening with a combination of ECG and NT-pro-BNP was always less cost-effective than using either of the initial tests alone, and both were less cost-effective than using a hand-held ECHO. [555]

The authors concluded that performing both ECG and NT-pro-BNP did not provide additional cost-savings and that utilizing the NT-pro-BNP may be preferred because of ease of interpretation and practicality. Additionally, these authors concluded that their study supports the development of community screening programs to screen high-risk patients (patients with ≥ 1 risk factor) for systolic dysfunction and the most cost-effective strategy would be a multi-step process to pre-screen using either ECG or NT-pro-BNP, followed by a hand-held ECHO in patients with abnormal results, in-turn followed by a traditional ECHO for those with abnormal hand-held ECHO results. [556]

Nielson and colleagues had similar conclusions after retrospectively examining the cost of using BNP to screen and detect LV dysfunction in the general population (n = 1,257). Patients completed a self-administered questionnaire and had blood pressure measured. All patients also received an ECG, an ECHO, and BNP measurement. Patients were categorized into three risk groups. The first group consisted of patients with symptomatic ischemic heart disease (IHD) (n = 140) who had either a self-reported history of MI and ischemic changes on ECG, or physician-diagnosed angina and were receiving therapy. The remaining patients were then categorized into two groups (high- and low-risk) where group assignment depended on the patients' blood pressure measurement and ECG reading. The high-risk patients (n = 269) had a blood pressure measurement greater than 160/95 and /or signs of ischemia on ECG. The low-risk group (n = 823) were without either of those conditions. There was a total of 48 patients (3.8%)

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[555] Ibid.

[556] Ibid.

with LV systolic dysfunction, 6 (0.7%), 16 (6%) and 26 (19%) in the low, high, and IHD groups respectively. BNP was significantly associated with LV systolic dysfunction in both the high-risk (p = 0.023) and IHD patients (p = 0.015) but not in low-risk patients (p = 0.087). [557]

The authors used a cost of $100 for ECHO and the cost of BNP was varied using values of $5, $10 and $20. The authors compared the cost per detected case of using an ECHO alone for all patients in each risk group with the cost of pre-screening with BNP (which consisted of BNP testing and subsequent ECHO for all patients with BNP levels ≥ 8 pg/mL). The cost per detected case of LVSD was less in all risk groups for all three cost values of the BNP assay. The cost per detected case via ECHO was $13,717, $1,681 and $538 for low-risk, high-risk and IHD groups respectively. The cost per detected case utilizing BNP ranged from $7,543 to $10,012 (cost-reduction range from 27- 45%) for low-risk, $1,243 to $1,512 (10 - 26%) for high-risk, and $442 to $529 (2 - 18%) for IHD. The authors did note that their proposed strategy would fail to detect LVSD for 1 in 6, 1 in 16, and 2 in 26 patients in the low-risk, high-risk and IHD group respectively. These authors concluded that using BNP levels to determine which patients to refer for an ECHO is cost-effective and that a questionnaire and blood pressure measurements are useful as "rule-outs" for LVSD. [558]

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[557] O. W Nielsen et al., "Retrospective Analysis of Thecost-effectiveness of Using Plasmabrain Natriuretic Peptide Inscreening for Left Ventricularsystolic Dysfunction in the General Population," *Journal of the American College of Cardiology* 41, no. 1 (2003): 113–120.
[558] Ibid.

3.4.2 ECONOMIC IMPLICATIONS IN CARDIOTOXICITY

In an early investigation of patients receiving doxorubicin, by Bristow and colleagues, authors compared the incidence of heart failure, heart failure mortality, and severity between patients receiving cardiac monitoring and those who did not. The monitoring protocol changed after data collection already started. The initial protocol included both invasive (biopsy and catheterization) and non-invasive (ECHO and systolic time interval via ECG) testing at mid-course with an optional measure at baseline. The new protocol required tests both at baseline and at regular intervals during therapy. [559]

Heart failure was defined as the development of symptoms suggestive of myocardial dysfunction verified via radiography or catheterization and biopsy. An abnormal ECHO was defined as a decrease in fractional shortening > 25% or decrease of > 10% to a value below 30%, abnormal septal thickening, or enlargement of either the left or right ventricles. Biopsy results were graded on a scale ranging from zero (no cell changes) to three (diffuse cell damage). There were 206 patients enrolled, 80 received monitoring (Group B), the remaining 126 had therapy guided by empiric dose limitations of doxorubicin (Group A). Group B (61%) had more patients with risk factors than Group A (46%), which included mediastinal radiation, history of hypertension, cardiomyopathy, coronary artery disease, valvular heart disease, age over 70 years and cumulative doxorubicin dose over 550 mg/m^2. [560]

Of the 206 patients, 15 patients developed heart failure, twelve of whom were in Group A, ten (of 15) had at least one risk factor and six of which died as a result of heart failure related causes (five deaths were in patients with risk factors). Of the three patients in Group B who developed heart failure, all possessed at least one risk factor. There was

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[559] Bristow, Mason, and Daniels, "Monitoring of Anthracycline Cardiotoxicity."
[560] Ibid.

not a significant difference in the incidence or HF mortality between groups, with or without regard to risk factors. Cost analysis was performed for the 49 patients with risk factors that were monitored, costs were based on billing fees charged by the health care facility and included the cost of performing tests and analyzing/interpreting results. The fees for biopsy and catheterization were $1,753 per test, systolic time interval was $55 per test, and ECHO was $108 per test. The authors "put these costs in perspective" by comparing the cost of monitoring to the cost of the actual chemotherapy, which has a 1979 price of $1.70/mg and averaged $1,122 per patient. The cost of monitoring averaged $2,209 per patient which translated to a cost of $20,308 and $25,650 per case of heart failure prevented and heart failure death prevented respectively. [561]

There were eleven patients who had false positive results on non-invasive testing who had subsequent invasive tests accounting for $19, 287 (18%) of the total monitoring costs ($108,245). The authors remarked that although cardiac monitoring is costly, it is a small fraction of the total cost of cancer care.[562] These authors conclude that patients without risk factors have a low incidence of heart failure and monitoring in this group would not be justified; however, incidence is high enough in patients with risk factors to justify cardiac monitoring. Further studies need to be conducted to find suitable non-invasive tests with higher sensitivity and specificity for cardiac monitoring. [563]

Shureiqi and colleagues created a decision analysis model to determine the cost-effectiveness of MUGA monitoring in patients receiving doxorubicin therapy. These authors pointed out that previously accepted guidelines for monitoring LVEF failed to account for the dose of doxorubicin received and the age of the patient. The model

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[561] Ibid.
[562] Ibid.
[563] Ibid.

covered five years, probabilities for heart failure with and without MUGA scanning, heart failure after doxorubicin therapy, five-year survival for non-Hodgkin's lymphoma, five-year survival for heart failure, and five-year survival from other causes were obtained from previously published studies. The probabilities for positive MUGA results were obtained from prospectively collected data from The University of Michigan. [564]

The cost of a MUGA scan used in the model was the facility charge-list price at the University of Michigan Medical Center in 1996, which was $751. The cost of patient time was estimated at three hours multiplied by the average wage of each age group as per a previously published population survey. The cost of heart failure was considered for the five years of the model, and was obtained from a published cost-effectiveness analysis using standard therapy plus enalapril [the previously published study reported a ten-year cost of $8,117 in 1992 dollars with a 5% discount rate]. The 1996 study used a 3% discount rate and used a five-year cost for heart failure therapy of $6,885. The costs of doxorubicin and non-doxorubicin-based chemotherapy were considered equal. The non-doxorubicin chemotherapy regimen was estimated to have a five-year recurrence rate of 26%, and the cost of additional high-dose salvage chemotherapy was $45,792. There were 227 patients screened using MUGA scans, 47 (21%) were between 15 - 39 years old, 98 (43%) were between 40 and 59 years old, and 82 (36%) were 60 and older. [565]

There were only four abnormal screens; one in the youngest group [was considered a false-positive], one in the middle-aged group, and two in the oldest group. Both cost-effectiveness and the probability of five-year survival based on the cumulative doses of 350 mg/m^2 and 500mg/m^2 were calculated and dependent on age. For the base-

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564 Shureiqi et al., "Clinical and Economic Impact of Multiple Gated Acquisition Scan Monitoring During Anthracycline Therapy."
565 Ibid.

case dose of 350 mg/m^2, the mortality gains were minor with survival improvements of less than 1.5% in each age group. The incremental mortality improvements with the higher dose were 0.77%, 2.12% and 2.7% for 15 - 39 years, 40 - 59 years and ≥ 60 years respectively. Cost-effectiveness ratios for each life-year saved for each of the three age groups were $425,402, $138,191 and $86, 829. [566]

The authors concluded that their findings may improve the monitoring guidelines regarding the use of MUGA scans. Additionally, they concluded that the cost-effectiveness of MUGA monitoring is dependent upon patient age and the cumulative dose of doxorubicin received. The use of MUGA pre-screening for patients under the age of 40, without evidence of cardiovascular disease, who received doses less than 350 mg/m^2 provides little benefit. They commented that since cardiotoxicity can manifest many years after treatment has ended and MUGA has low sensitivity to detect dysfunction in this setting, more sensitive methods should be used. [567]

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[566] Ibid.
[567] Ibid.

3.5 Summary of Chapter Three

Heart failure in breast cancer patients is a significant adverse effect of the most active regimens used to treat the disease. While there are conflicting estimates of its incidence and prevalence, heart failure as an outcome is treatable with appropriate medications. If HF is discovered early enough, it could potentially be reversible.

There are many barriers to the effective monitoring of cardiac function in breast cancer patients who have received cardiotoxic treatments. The monitoring costs prove to be a significant barrier. Numerous studies have evaluated the utility of BNP levels heart failure assessment and treatment, and reported similar conclusions. BNP is an adequate tool to discriminate between patients with LV dysfunction and those without. There have been additional studies that suggest cardiac troponins are the blood levels that should be monitored with respect to chemotherapy-induced heart failure. Although the costs of troponin levels are in-line with the cost of a BNP test, troponins may require multiple draws to get a post-therapy level, which make this test a less attractive alternative when compared to BNP.

There have been studies examining the cost-effectiveness of BNP in both population screening and in patients with cardiac known disease. While those studies were primarily examining heart failure independent of cancer treatment, similar principles would apply. If heart failure, either with or without cancer treatment is not diagnosed early, the patient may experience an acute decompensated episode. The studies reported that BNP monitoring saved resources when differentiating patients with acute symptoms.

With the availability of BNP rapid assays at considerably lower costs than either invasive biopsies or expensive radiological procedures, guidelines for cardiac monitoring

can be followed in the clinical practice setting (not only in clinical trials) and could ultimately decrease hospitalizations and mortality in these patients.

CHAPTER FOUR: METHODOLOGY

4.1 Introduction

This chapter will provide details of the study methodology. Section 4.1 includes the purpose of the study and problem statement, study objectives with corresponding hypotheses to be tested. Section 4.2 gives an introduction to the economic evaluation in healthcare, welfare/extra-welfare and Pareto economics, an introduction to patient preferences and outcome measures, and types of analyses. Section 4.3 discusses cost-effectiveness analyses in more detail as well as the use of decision analysis and Markov analyses, including the rationale for using decision analysis/Markov modeling, and the strengths and weaknesses of specific modeling methods. Section 4.4 gives an introduction to uncertainty and sensitivity analyses and section 4.5 gives an introduction to utilities and health-related quality-of-life.

Section 4.6 gives the specific estimates and parameters used for the model in this study. This includes the study perspective, the inclusion/exclusion criteria for the hypothetical cohort, details regarding costs included, sources and calculation of probability estimates. Additional parameters included the incidence and prevalence of heart failure in breast cancer patients as well as utility estimates for heart failure patients, these data were obtained either from previously published literature or calculated with estimates given by SEER. This chapter concludes with additional model considerations, which includes figures illustrating the proposed model structure of relevant decision and chance nodes as well as heart failure transition states used in the study, details regarding cycle length and termination conditions, and discussion of model assumptions.

4.2 Study Objectives and Hypotheses

4.2.1 STUDY OBJECTIVES

From the review of the literature, it is clear that although it has been known that cancer patients often develop heart failure, strategies for earlier detection and diagnosis are needed. Numerous studies examining the use of BNP and/or NT-pro-BNP assays for screening populations for heart failure suggest that both tests have the potential to fulfill this need and could be cost-effective for this purpose. This dissertation will evaluate the cost-effectiveness of these tests when compared with strategies currently employed.

The objectives of the study are as follows:

1. Describe current cardiotoxicity-induced heart failure monitoring strategies used in breast cancer patients.
2. Estimate the current incidence of treatment-induced heart failure in breast cancer patients.
3. Estimate costs of performing heart failure monitoring using B-type Natriuretic Peptide, ECHO, or MUGA scanning at frequencies determined by NCCN surveillance guidelines.
4. Estimate average direct costs of treating heart failure in patients diagnosed as a result of monitoring.
5. Estimate differences average in QALYs for each monitoring option
6. Calculate the incremental cost-effectiveness of using BNP monitoring versus no monitoring, ECHO, or MUGA scanning; effectiveness will be measured as percent diagnosed.
7. Calculate the incremental cost-utility of using BNP monitoring versus no monitoring, ECHO, or MUGA scanning; utility measured as QALYs.

4.2.2 EXPANSION AND HYPOTHESES

The literature review suggests that although ECHO has been the more widely accepted method for monitoring cancer patients for the development of heart failure, the use of BNP may provide a more cost-effective alternative to what is currently considered the "gold-standard". Expanded explanation of the objectives and specific hypotheses, where applicable, are outlined below.

Objective one was to describe the currently employed strategies to monitor for chemotherapy-induced heart failure. Strategies used are mentioned in the NCCN Breast Cancer guidelines and are described in detail in the ACC/AHA Heart Failure guidelines. No hypothesis needs to be tested for this objective.

Objective two was to estimate the current incidence of treatment-induced heart failure in breast cancer patients. The development of heart failure is known to be related to the regimen received, it is also known that patients receiving therapy corresponding to testing HER-2 positive (e.g., trastuzumab) have higher incidence of heart failure than patients treated with chemotherapy alone (e.g., cyclophosphamide and doxorubicin). Therefore, incidence of heart failure will be therefore determined from widely accepted values reported in the literature for a hypothetical cohort of U.S. breast cancer patients diagnosed and successfully treated (i.e., survived to achieve complete remission) for invasive disease in 2010. The estimated number of new cases of breast cancer for all ages and races is available from SEER; therefore, no hypothesis needs to be tested for this objective. [568]

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[568] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

Objective three was to estimate the costs of using each monitoring strategy to be compared at follow-up intervals suggested by current surveillance guidelines. Surveillance is performed by the treating oncologist to monitor for not only cancer recurrence but also for late-onset adverse reactions to therapy. ASCO recommends that patients have a follow-up visit every three to six months for the first three years after adjuvant treatment, then every six to twelve months for the next two years and annually thereafter. [569] NCCN guidelines recommend a follow-up visit every four to six months for the first five years then annually thereafter. [570] There is a risk of breast cancer recurrence for up to fifteen years after initial adjuvant therapy, and heart failure can develop at any point in that period; therefore, total costs will be determined corresponding to that surveillance period.

Objective four was to estimate the average direct cost of treatment of heart failure that is discovered and diagnosed as a result of monitoring. The treatment scenarios for different stages of heart failure were obtained from ACC/AHA guidelines for treatment. Costs will include the direct costs of medications used in both asymptomatic and symptomatic stages, costs of emergency care and/or hospitalizations resulting from heart failure exacerbation, and costs of outpatient cardiology management. Since the perspective of the study is the payer, MAC unit cost will be used to represent the costs of medications. Costs of emergency care and/or hospitalizations and outpatient management were obtained from published literature and/or CMS. The hypothesis tested for this objective is that the average direct costs of treating cardiac dysfunction as a result of BNP

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[569] Khatcheressian et al., "American Society of Clinical Oncology 2006 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting."

[570] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

will be greater than the strategy of doing nothing, but less than using either ECHO or MUGA.

- No Monitoring $_{direct\ cost}$ < BNP $_{direct\ cost}$

- BNP $_{direct\ cost}$ < ECHO $_{direct\ cost}$

- BNP $_{direct\ cost}$ < MUGA $_{direct\ cost}$

Objective five was to estimate any differences in QALYs between each monitoring strategy. Utilities for patients with heart failure are readily available in published literature. The difference in utilities will arise from the stage of heart failure at diagnosis and subsequent transitioning through progressive states. The hypothesis for this objective is that the QALY associated with the use of natriuretic peptides is greater than the options being compared (i.e. doing nothing, ECHO and MUGA).

- No Monitoring $_{QALY}$ < BNP $_{QALY}$

- ECHO $_{QALY}$ < BNP $_{QALY}$

- MUGA $_{QALY}$ < BNP $_{QALY}$

Objective six was to determine the incremental cost-effectiveness of using BNP versus other comparators; effectiveness measured by the percent of patients diagnosed. The hypothesis for this objective is the percentage of patients' diagnosed utilizing BNP will be greater than that of either ECHO or MUGA. Since the average costs associated with BNP are expected to be lower, the resulting ICER will show that BNP is the dominant strategy.

- ECHO $_{\%\ Diag}$ < BNP $_{\%\ Diag}$

- MUGA $_{\%\ Diag}$ < BNP $_{\%\ Diag}$

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Objective seven was to determine the incremental cost-utility of using BNP versus other comparators as measured by QALYs. The Hypothesis for this objective is the ICER resulting from the comparison of all alternatives to BNP will be below the WTP threshold of $50,000.

- BNP vs. No Monitoring; ICER < $50,000 WTP per QALY

- BNP vs. ECHO; ICER < $50,000 WTP per QALY

- BNP vs. MUGA; ICER < $50,000 WTP per QALY

4.3 Theoretical Basis of Economic Evaluation of Healthcare

4.3.1 INTRODUCTION TO ECONOMIC EVALUATION IN HEALTHCARE

Economic evaluation is important in healthcare as resources are finite; therefore, to facilitate the most efficient utilization, it is important to have analyses that evaluate all of the relevant choices available. Since each alternative may yield differing outcomes, it is imperative that analyses account for a variety of end-points. There are two characteristics of economic evaluation; economic evaluation considers both inputs and outputs, and is concerned with choices. Drummond et al. define economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences". [571]

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[571] Michael Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes* (Oxford University Press, USA, 2005), http://www.amazon.ca/exec/obidos/redirect?tag=citeulike09-20&path=ASIN/0198529457.

4.3.2 WELFARE/PARETO ECONOMICS

There are different perspectives from which to perform economic evaluations including that of society, the payer, or patient. In the societal perspective, the goal is to improve welfare for everyone in the society. Welfare economics is described as "achieving a social maximum derived from individual desires" and is based on the assumptions that individuals will maximize preferences represented by utility functions and overall welfare is a function of those individual preferences. Utility is considered the only outcome of interest and societal welfare is the sum of all individual's welfare and the affected individuals are the source of how utility is valued. [572] Preferences of individuals are typically determined by how those individuals prioritize health status over other goods and services; social utility is the synthesized composite of all the individual utilities. [573]

Economic analyses often take the perspective of society; Pareto economics is a type of welfare economics which considers those preferences and is one method to aggregate utilities among individuals to determine if the proposed resource allocation will improve social welfare. When creating an aggregate utility representing individuals, there are a number of states that can result depending on whether members of society gain or lose utility. Resulting states include optimality, improvement, efficiency, deterioration, comparable, and non-comparable. [574]

Pareto optimality exists when the demands of society do not exceed supply and is broken down into improvement and efficiency. An improvement is when the allocation of

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[572] Werner B. F. Brouwer et al., "Welfarism Vs. Extra-welfarism," *Journal of Health Economics* 27, no. 2 (March 2008): 325–338.

[573] Michael Drummond and Alistair McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice* (New York: Oxford University Press, 2001).

[574] Ibid.

resources improves the utilities of all, (the opposite of this would be Pareto deterioration). Pareto efficiency is when there is improvement in utilities for some; however, no one is worse off. The status of how "well-off" someone is can be measured in either tangible goods or in natural units (such as life-years or health). Pareto non-comparable states occur when there are some that gain utilities and some lose in re-allocation. [575]

The figure below (Figure 4.1) illustrates the comparison of utilities between two individuals and the gains and losses as there are transitions between states. In the figure, each axis represents levels of utilities with respect to two individuals, the lower case letters in each quadrant serve to represent the gain or losses in utilities from one level to another. In the figure, point e represents the initial allocation of resources. Quadrants A and D correspond to Pareto non-comparable states since moving from the initial allocation (e) into either results in one person gaining while the other loses (i.e., a move to either points x or z, result in a situation where one individual clearly gains utility while the other loses). Whereas moving to points y or w creates a gain or loss for both individuals respectively. [576]

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[575] Ibid.

[576] Ibid.

Figure 4.1 Transitioning Pareto States [577]
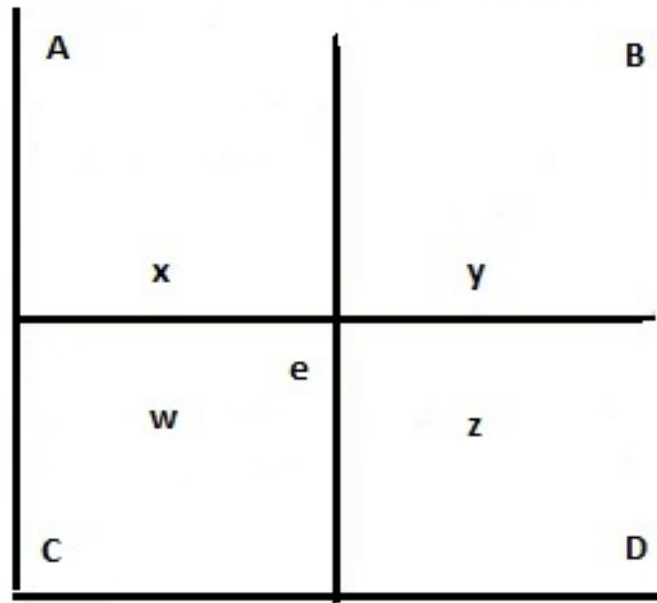
4.3.3 EXTRA-WELFARISM

Not unlike welfare economics, extra-welfarism considers utilities and preferences, but also allows the inclusion and consideration of other outcome measures important for well-being such as health gained, patient satisfaction, and the burden on caregivers. As a result, those additional individuals such as caregivers, health care providers, experts or decision makers can be a source of how outcomes will be valued. Individual weights are assigned to outcomes of interest (such as QALYs); therefore, extra-welfarism provides a

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[577] Ibid.

mechanism where outcomes such as health gained can be compared among individuals.
[578]

4.3.4 PREFERENCES/UTILITIES

Preferences or utilities "refer to the level of subjective satisfaction, distress, or desirability that people associate with a particular health state." [579] Utilities can also be considered a measure of health based on how individuals prefer one health state over another. [580] Approaches to determine preferences typically involve a sequence of general steps including: defining the health states of interest; identifying subject(s) to assign ranks or weights to the chosen health states; and compiling those rankings to determine an overall scale-value for each respective health state. [581] When measuring health states, it is important to determine: which dimensions of that state will be considered relevant (such as physical or social functioning); which scaling method will be used; how material will be presented to subjects; and potential population or situational differences that may affect responses. [582]

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[578] Brouwer et al., "Welfarism Vs. Extra-welfarism."

[579] Debra G. Froberg and Robert L. Kane, "Methodology for Measuring Health-state preferences--I: Measurement Strategies," *Journal of Clinical Epidemiology* 42, no. 4 (1989): 345–354.

[580] Ann M. Holmes, "A Method to Elicit Utilities for Interpersonal Comparisons," *Medical Decision Making* 17, no. 1 (February 1, 1997): 10 –20.

[581] Froberg and Kane, "Methodology for Measuring Health-state preferences--I: Measurement Strategies."

[582] Ibid.

4.3.5 OUTCOME MEASURES

The outcomes from a given intervention can be measured in reduced mortality or morbidity; these alone do not incorporate the impact the health state has on someone's life. Measures which incorporate individuals' preferences for particular health states include measures such as quality-adjusted life-years (QALYs) or healthy-year equivalents (HYEs) which incorporate quantity of life gained as well as health-related quality of life (HRQoL). Quality-adjusted life-years (QALYs) are a single measure that represents not only the quantity of time that can be gained from reduced morbidity and mortality resulting from an intervention, but also how incorporates the "quality" of that time by accounting for patient preferences. This approach assigns a value (usually between zero and one, however states worse than death are also recognized, which yield a negative value) corresponding to the HRQoL for a given year. QALYs are obtained by multiplying the established utility for a particular health state by the amount of time spent in that state. Healthy-year equivalents (HYEs) determine how many years of perfect health subjects would consider equivalent to a particular health state. [583]

Other valuation methods can be used to determine patient preferences for health states and to quantify how individuals value the benefits gained from health care improvement or interventions (including monetary value). Valuation methods that can be used to elicit preferences include either interval or ratio scales; both are considered to add comparability among individuals. [584] The scaling method chosen by researchers is based

583 Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.
584 Debra G. Froberg and Robert L. Kane, "Methodology for Measuring Health-state preferences--II: Scaling Methods," *Journal of Clinical Epidemiology* 42, no. 5 (1989): 459–471.

on how measurements are collected from respondents (i.e., how questions are presented to respondents) and how the data will be aggregated. [585]

Methods with interval-level data include the standard gamble (SG), time-trade-off (TTO) and visual or rating scales; these methods ask respondents to assign a value on one health state in comparison to another. In the standard gamble (SG) method, respondents are asked to choose between two alternatives, with either definite or variable outcomes (like a wager). The subject could be given alternatives that may represent different therapies where one choice would cause certain death, the other could either lead to absolute perfect health or a state that is considered worse than the certain outcome (in this case, worse than death). [586] The time-trade-off (TTO) method is similar to SG, except that all outcomes are certain. Respondents essentially have to quantify how much time they would sacrifice to be in a state that is healthier than another (i.e., respondents can choose to be in some chronic disease state for the typical life expectancy for that condition or give up some of that life expectancy to be in a healthier state). In visual analog (VAS) or rating scales, the respondents are shown a line or continuum with definite anchors on each end, such as death and perfect health. Respondents are then asked to place various health states with representative differences between states. Subjects could also be presented with a line with existing graduations on it and asked to sort a group of states into categories. [587]

Valuation methods with ratio-level data ask respondents to quantify how much better or worse one state is compared to another. These include magnitude estimation, equivalence and willingness-to-pay (WTP). In magnitude estimation, respondents are

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585 Froberg and Kane, "Methodology for Measuring Health-state preferences--I: Measurement Strategies."
586 Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*;
Froberg and Kane, "Methodology for Measuring Health-state preferences--I: Measurement Strategies."
587 Froberg and Kane, "Methodology for Measuring Health-state preferences--II: Scaling Methods."

first given a state that they will use as a standard for comparison purposes. They will then be given other states to provide a number or ratio of how much better or worse that state is compared to the standard.[588] The equivalence method is similar to magnitude estimation in that respondents are given a standard health state for comparison purposes and a specified number of people in that state. They are then presented with other health states and asked to estimate how many people in that state would be equivalent to the number in the reference.[589] For example, if the reference state is perfect health which has 50 people, respondents could be given various states of lesser health and asked to assign a number ≥ 50 representing the quantity of people in each state that would be equal to those in perfect health.

In the willingness-to-pay (WTP) method, respondents are asked to give either a dollar amount or proportion of income they would pay for a particular intervention to gain a certain level of improvement in health. [590] Positive aspects of the WTP method are that the respondents are valuing the benefits in the same units as costs and are not restricted in considering only the health-related benefits. WTP can be assessed using contingent valuation (CV), conjoint analysis/discrete choice experiments (CA/DCE) or magnitude estimation. [591]

Contingent valuation (CV) specifically asks respondents to quantify the maximum amount they would be willing-to-pay for a particular health benefit, or the minimum amount they would be willing-to-accept (WTA) to forego that benefit. [592] In order for CV

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588 Ibid.

589 Ibid.

590 Ibid.

591 J. A. Olsen and R. D. Smith, "Theory Versus Practice: a Review of 'willingness-to-pay' in Health and Health Care," *Health Economics* 10, no. 1 (2001): 39–52.

592 Tapio Nousiainen et al., "Concomitant Impairment of Left Ventricular Systolic and Diastolic Function During Doxorubicin Therapy: A Prospective Radionuclide Ventriculographic and Echocardiographic Study," *Leukemia & Lymphoma* 43 (January 2002): 1807–1811.

to be useful, it is crucial that both the hypothetical scenarios surrounding health states/benefits and how payments are made are carefully defined. [593] Conjoint Analysis (CA) (also known as discrete choice experiments) utilizes ranking, rating or pairwise comparisons to determine how a respondent values particular attributes of health states. CA can be used to determine values for both WTP and QALY depending on the attributes to which respondents are assigning values. [594]

4.4 Types of Analyses

There are a number of methods which to perform such comparisons; those include cost-minimization, cost-effectiveness (CEA), cost-benefit (CBA), and cost-utility analyses (CUA). Each technique has a distinct approach to account for the costs and consequences of the alternatives being compared. [595] Table 4.1 illustrates the different types of analyses that can be performed which are classified as either partial or full analyses. A partial analysis may consider one or multiple alternatives and can describe, quantify or compare either outcomes or costs. Typically, partial analyses take one of the following approaches: describe outcomes or costs of a single alternative; compare either costs or outcomes for multiple alternatives; or describe both costs and outcomes for a single alternative. Full analyses include comparisons of both costs and consequences of

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[593] Richard T. Carson, "Contingent Valuation: A User's Guide†," *Environmental Science & Technology* 34, no. 8 (April 1, 2000): 1413–1418; Richard D Smith, "Construction of the Contingent Valuation Market in Health Care:a Critical Assessment," *Health Economics* 12, no. 8 (August 1, 2003): 609–628.

[594] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*; Terry N. Flynn, "Using Conjoint Analysis and Choice Experiments to Estimate QALY Values: Issues to Consider.," *PharmacoEconomics* 28, no. 9 (2010): 711–722.

[595] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.

multiple therapies or interventions; examples of full analyses include cost-benefit, cost-effectiveness and cost-utility analyses. [596]

Table 4.1 Types of Economic Analyses [597]

		Are Both Costs and Consequences Examined?		
		No		*Yes*
		Consequences Only	*Costs Only*	
	No	**1A Partial Evaluation** Outcome Description	**1B Partial Evaluation** Cost Description	**2 Partial Evaluation** Cost-Outcome Description
	Yes	**3A Partial Evaluation** Efficacy or Effectiveness Evaluation	**3B Partial Evaluation** Cost Analysis	**4 Full Evaluation** CEA CBA CUA

*(Row header spanning both data rows: **Two or More Alternatives?**)*

CEA: Cost-Effectiveness Analysis; CBA: Cost-Benefit Analysis;
CUA: Cost-Utility Analysis

Cost-minimization analyses (CMA) consider the outcomes to be equal among alternatives; therefore, the only real comparison is the cost of that intervention or therapy. This may, for instance, be a comparison of medications for hypertension within the same drug class that have both been shown have similar decreases in blood pressure. Cost-

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[596] Ibid.
[597] Ibid.

benefit analyses (CBA) consider the costs of the interventions being compared and also assign monetary values to the gains expected. These analyses can be useful to decision makers who are comparing programs that have very different outcomes, and because of budgetary restraints, resources can only be applied to the adoption of a single alternative. [598]

In cost-effectiveness analyses (CEA), the inputs of an intervention are assigned a monetary value or cost, and outcomes or consequences are expressed in units of improvement or gain (i.e., decrease in mmHg); the alternatives being compared must have similar outcome measures. Results of cost-effectiveness analyses are expressed as cost-effectiveness ratios (CERs) or incremental cost-effectiveness ratios (ICERs) which enable the decision maker to compare alternatives to either each other or to a threshold value. [599] Cost-utility analyses are similar to CEA; however, the outcomes have been assigned a value or utility based on preferences of the patients. The outcomes of each alternative are often expressed in quality-adjusted life years (QALYs). [600]

4.4.1 COST-EFFECTIVENESS ANALYSES

As previously mentioned, there are a number of methods available to evaluate alternatives in economic terms to assist decision makers in the allocation of resources. Cost-effectiveness analysis (CEA) is one method. [601] In CEA, the costs or resources required for each alternative or intervention designed to improve health are expressed in

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[598] Ibid.

[599] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*; Marthe R. Gold et al., eds., *Cost-effectiveness in Health and Medicine* (Oxford University Press US, 1996).

[600] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.

[601] Ibid.

monetary terms such as U.S. dollars. The consequences or outcomes of each alternative are expressed in natural units representing the improvement in health as a result of that intervention.[602] Comparisons between competing alternatives can be made with the resulting cost for each unit gained in improved health. These are often expressed as cost-effectiveness ratios (CERs) in which each alternative is compared to no intervention, or incremental cost-effectiveness ratios (ICERs), which directly compares the alternatives to each other. The ICER takes the differences in cost between two alternatives and divides that by the difference in the units of effectiveness. [603]

$$\textbf{ICER} = \frac{\Delta\textbf{Costs}}{\Delta\textbf{Effectiveness}}$$

The resulting ICER can be displayed in a grid or plane for interpretation purposes as illustrated in Table 4.2 and Figure 4.2, respectively. When comparing two competing alternatives (for example Drugs A and B), there can be one of four potential results; drug A costs more and is more effective, costs more but is less effective, costs less and is less effective, costs less and is more effective. Results can then be expressed in a cost-effectiveness grid or plane. [604]

For illustration purposes, Table 4.2 shows the comparison of two alternatives, drugs one and two. Drug one can be a medication recently approved for use, and Drug

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[602] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*; Gold et al., *Cost-effectiveness in Health and Medicine*.

[603] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.

[604] J.L. Bootman, R.J. Townsend, and W.F. McGhan, *Principles of Pharmacoeconomics*, 3rd ed. (Cincinnati OH: Harvey Whitney Books Co., 2005); K. L. Rascati, *Essentials of Pharmacoeconomics* (Philadelphia: Wolters Kluwer Health, 2009).

two can be the older, standard alternative and can be considered the "gold-standard" and the baseline for comparison. The darker gray areas of the grid represent scenarios where the new alternative (1) is dominated by the standard alternative (2) in that it either has equal costs with lower effectiveness or equal/ lower effectiveness with higher costs. [605] The lighter gray squares represent scenarios where the newer alternative (1) would dominate over the standard alternative in that it has lower costs with equal or higher effectiveness, or equal costs with higher effectiveness. [606]

Table 4.2 Cost-Effectiveness Grid[607]

		Costs		
		Lower	**Equal**	**Higher**
Effectiveness	**Lower**	A	B	C
	Equal	D	E	F
	Higher	G	H	I

In Figure 4.2, the vertical and horizontal axes represent a continuum of costs or effectiveness respectively, and the origin is the point where costs and/or effectiveness would be equal among the alternatives. Each quadrant of the plane represents how the differences in costs and effectiveness between the comparator and traditional, baseline or

[605] Bootman, Townsend, and McGhan, *Principles of Pharmacoeconomics*; Rascati, *Essentials of Pharmacoeconomics*.
[606] Rascati, *Essentials of Pharmacoeconomics*.
[607] Ibid.

"gold standard" alternative. There are two quadrants where one alternative will clearly dominate the other (II and IV) and two quadrants (I and III) where the decision maker must determine which they value more, greater effectiveness or lower costs. Quadrant II represents a scenario where the newer alternative costs less and has greater effectiveness thus dominating the baseline alternative. Results in quadrant IV represent the opposite scenario in which the newer alternative would both cost more and have lower effectiveness; thus, it is dominated by the older or standard therapy. [608]

In quadrants I or III, it would be up to the discretion of the decision-maker or stakeholder whether they value the lower cost or higher effectiveness. Quadrant I is a scenario where the newer alternative costs more but is also more effective; Quadrant III is the opposite scenario in which the newer alternative costs less but is also less effective. [609]

[608] Bootman, Townsend, and McGhan, *Principles of Pharmacoeconomics*; Rascati, *Essentials of Pharmacoeconomics*.

[609] Bootman, Townsend, and McGhan, *Principles of Pharmacoeconomics*; Rascati, *Essentials of Pharmacoeconomics*.

Figure 4.1 Cost-Effectiveness Plane[610]

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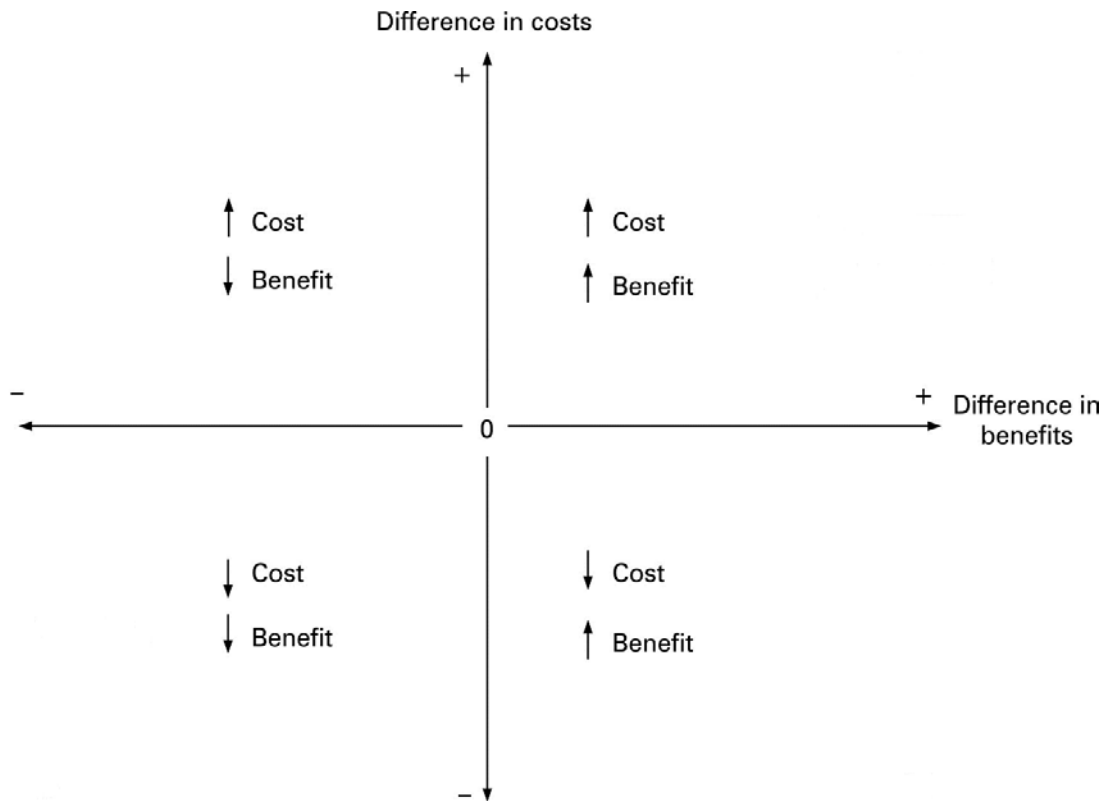
[610] Bootman, Townsend, and McGhan, *Principles of Pharmacoeconomics*.

Advantages of CEA include the use of clinical natural units as the outcomes of interest which are often metrics that healthcare practitioners and decision makers already use and are already familiar with. Additionally, assigning monetary values to outcomes is not required. Critics of CEA frequently cite a limitation that CEA does not address social welfare issues that can be addressed with other methods. [611]

4.4.2 DECISION ANALYSIS

There are different types of decision analysis including decision trees and Markov models. [612] Decision trees are less complex forms of decision analysis but the concepts are similar. First, a question must be formulated that could be answered by the analysis, and there should be multiple alternatives in which to compare. A decision tree is then constructed such that each alternative being compared has a branch from the initial node which is a decision node signifying a choice between the alternatives. This node is illustrated with a square and there should only be a single decision node for each tree. [613] The subsequent nodes on each branch represent the probabilities of experiencing a particular outcome; these are chance nodes which are notated with circles. The end result of each branch, or terminal node, is represented by a triangle and signifies the outcome of each branch.

The outcomes can be measured in a number of units such as mortality, QALYs, symptom-free days or dollars. [614] The values at the end of each pathway comprise both

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[611] Gold et al., *Cost-effectiveness in Health and Medicine*.

[612] J. M Inadomi, "Decision Analysis and Economic Modelling: a Primer," *European Journal of Gastroenterology & Hepatology* 16, no. 6 (2004): 535.

[613] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*; Inadomi, "Decision Analysis and Economic Modelling."

[614] Inadomi, "Decision Analysis and Economic Modelling."

the cost and health effects of that respective intervention or alternative. [615] Once the model is structured, each chance node is assigned a probability. Then the analysis is performed by a procedure called folding back. The outcomes are multiplied by the probability of experiencing that outcome; these calculations continue from the right side of the tree to the left and these values are added together. After these values are obtained, sensitivity analysis is then performed in which one or more values in the model are varied to see if the end result stays consistent (i.e., is one alternative is found to be more cost-effective with the initial analysis, if after values in the model are varied, the same result is achieved, the analysis is insensitive, which is desirable). [616] Figure 4.3 summarizes the steps for constructing decision trees. [617]

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[615] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.

[616] Inadomi, "Decision Analysis and Economic Modelling."

[617] Xin Sun and Thomas Faunce, "Decision-analytical Modelling in Health-care Economic Evaluations," *The European Journal of Health Economics* 9, no. 4 (2007): 313–323.

Figure 4.3 Steps in Decision Analysis[618]
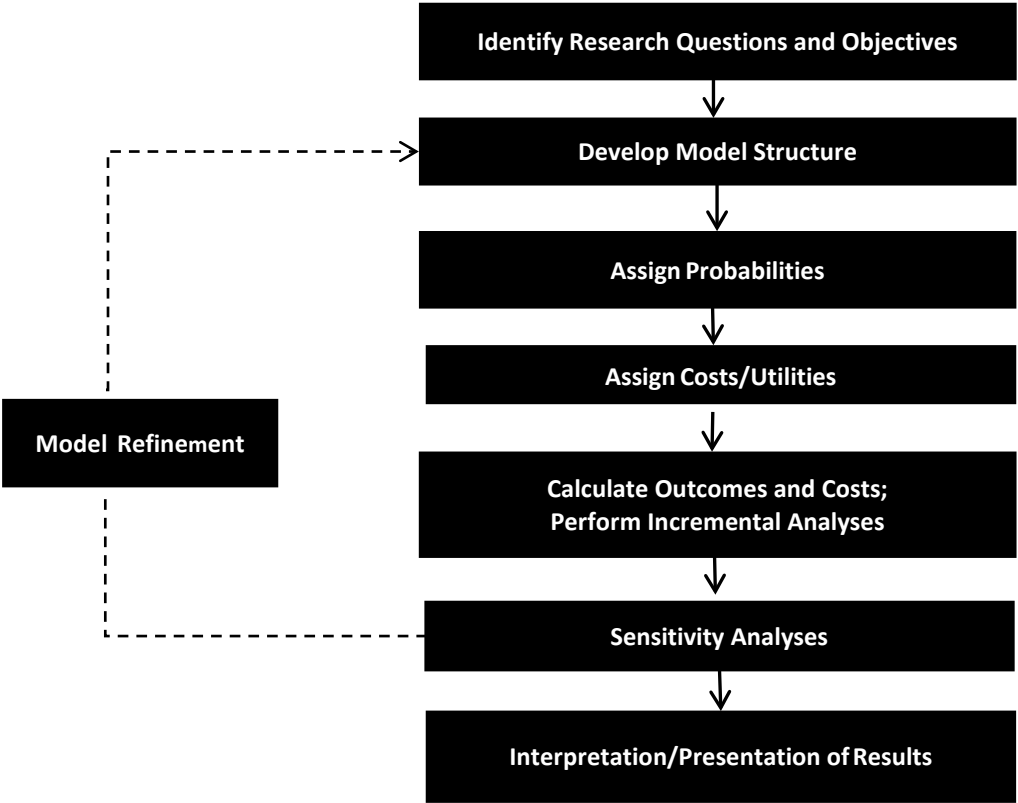
Limitations of decision analysis include: the dependence on initial assumptions; complex health states are simplified (i.e., chronic disease states often lead to complicated models); and the choice of which costs to include is somewhat arbitrary. Additionally, decision trees represent events that occur at a single time point; thus, time-dependent variables are difficult to incorporate into the model. [619]

4.4.3 MARKOV MODELING

In healthcare economics, a model is "any mathematical structure that represents the health and economic outcomes of patients or populations under a variety of scenarios." (Drummond and McGuire, 2001) A Markov model is essentially a repetitive decision tree. Markov models are useful when the risk of an event is ongoing, the timing of events is important, and in diseases where events can occur more than once. Markov modeling compensates for the limitations of decision trees since the method incorporates the stages of chronic diseases that patients can be in at any given time as well as the passage of time. [620]

To conduct an analysis with a Markov model, first, the health states under examination must be determined; these must include all relevant states associated with the disease and/or treatment over time. These are depicted in a transition state diagram representing the possible states along with arrows showing allowable transitions between

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[619] Alan Brennan and Ron Akehurst, "Modelling in Health Economic Evaluation: What Is Its Place? What Is Its Value?," *Pharmacoeconomics* 17, no. 5 (2000): 445; Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*; Inadomi, "Decision Analysis and Economic Modelling."

[620] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*; Inadomi, "Decision Analysis and Economic Modelling"; F. A. Sonnenberg and J. R. Beck, "Markov Models in Medical Decision Making: A Practical Guide," *Medical Decision Making* 13, no. 4 (1993): 322–338.

them. The transition between states can be in either direction which would indicate that someone can move from one health state to another and back again; however, patients can only reside in one health state at any given time. The exception is an absorbing state (i.e., death); once someone transitions to an absorbing state, transition to other states is no longer possible. Additionally, a state may have an arrow leading to back to that same state, which indicates that once someone reaches that health state, they may remain there. [621]

Temporary states and tunnel states may also exist in Markov models. A temporary state is used to represent states that have short-term effects such as a hospitalization. These states have arrows leading out since someone cannot remain in a temporary state for more than one cycle. These can be used to account for costs or utilities, and for the difference in transition probabilities which may differ if someone enters that state. Tunnel states can be considered a sequence of temporary states that occur in only a specified sequence. [622]

Like decision trees, once the model is constructed, inputs must have values assigned to them. Since Markov models account for time, the cycle length must be specified. Cycle length should realistically represent the time it would take to transition between the health states. Once that is determined, probabilities need to be assigned to each possible transition and the outcomes must be specified. In Markov Models, unlike decision trees where outcomes are only considered at the end, the outcomes are cumulative throughout the duration at the model. [623]

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[621] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.
[622] Ibid.
[623] Inadomi, "Decision Analysis and Economic Modelling."

Markov models can use either of two methods of evaluations, Monte Carlo simulations or cohort simulations. A Monte Carlo simulation has individual patients from the hypothetical cohort transition through model one at a time and the resulting outcome (such as QALY) is recorded for each individual. The overall outcome is determined by taking the average of those for all individuals. The advantages of Monte Carlo simulations are that states need only describe current clinical information because it allows past information to be tracked specifically for each patient transitioning through the model. The disadvantages are that the analysis takes longer to run and it is not considered as transparent as cohort simulations. [624]

Cohort simulations track the hypothetical cohort through model simultaneously; this produces a Markov trace which shows the movement of the cohort through the health states and the cumulative utilities and costs assigned. The model is run until entire cohort reaches the death (absorbing) state – after this cycle, the cumulative utility is the expected QALY of the cohort. While all members of the cohort begin the simulation simultaneously, they do not necessarily need to begin in the same health state. The advantages of cohort simulations are that they are faster to run, easier to debug, and are considered more transparent than Monte Carlo simulations. The disadvantage is that the state definitions need to include all of the relevant current and past clinical information, which can lead to extremely complex models. [625]

The advantages of using Markov models over decision analysis include the ability to transition between health states with representative probabilities of such transitions

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[624] Brennan and Akehurst, "Modelling in Health Economic Evaluation"; Andrew Briggs and Mark Sculpher, "An Introduction to Markov Modelling for Economic Evaluation.," *PharmacoEconomics* 13, no. 4 (April 1998): 397–409; Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.

[625] Briggs and Sculpher, "An Introduction to Markov Modelling for Economic Evaluation."; Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.

may make models more realistic, and the outcomes are cumulative throughout the duration of the model, whereas in decision analysis, the outcomes are only considered at the end. Disadvantages or limitations of using Markov models include: outcomes may be measured by surrogate markers in lieu of the actual outcome of interest; the data are from diverse sources that can be subject to an indeterminate amount of bias from confounding factors (i.e., the patient selection and methods of data analysis); and transition probabilities depend only on the state the patient is in at that point (i.e., states do not incorporate prior health information). Critics also often mention that Markov models have the potential for a lack of transparency (i.e., black-box). [626]

All of these limitations can be minimized by careful and detailed documentation of data sources and any assumptions that are made regarding the construction of the model. Sensitivity analyses also reduce bias from the selection of certain values over others for each parameter. [627]

4.5 Sensitivity Analysis/Assessment of Uncertainty

4.5.1 INTRODUCTION

"Uncertainty refers to the fact we can never know for certain what the mean (expected) costs and effects would be if the treatment is provided for a particular population of patients, even if they had the same observed characteristics." [628] When

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[626] Drummond and McGuire, *Economic Evaluation in Health Care : Merging Theory with Practice*.

[627] Ibid.

[628] Karl Claxton, "Exploring Uncertainty in Cost-Effectiveness Analysis.," *PharmacoEconomics* 26, no. 9 (June 2008): 781.

conducting decision analysis, it is preferred that the estimates for each parameter are obtained from published literature in which results are obtained from a study population with natural variation. However if obtaining estimates from published literature is not possible, the researcher may consult experts in the field for estimates. The estimates that are obtained from expert opinion have a degree of inherent uncertainty. Sensitivity analyses are used to examine such uncertainty. In sensitivity analyses, values for model inputs are varied to determine if calculations yield similar conclusions. [629]

There are four types of uncertainty in Markov models; those include parameter, analytical or methodological, structure or model, and generalizability. [630] Parameter uncertainty relates to estimates used as model inputs such as costs, transition probabilities and utility estimates. Analytical uncertainty refers to specific methods chosen such as costing, outcome measures, and cycle length and termination conditions. Structure uncertainty refers to model structure, specifically, how accurately the model represents disease progression. Generalizability refers to how well the included population represents the population the study is intended to effect. [631] These four types ultimately represent uncertainty in either the data used as input for the model or uncertainty relating to the model itself. [632]

[629] Gold et al., *Cost-effectiveness in Health and Medicine*.

[630] Sun and Faunce, "Decision-analytical Modelling in Health-care Economic Evaluations."

[631] Ibid.

[632] Gold et al., *Cost-effectiveness in Health and Medicine*.

4.5.2   TYPES OF SENSITIVITY ANALYSIS

Sensitivity analyses can be either deterministic or probabilistic. In deterministic analyses (or simple sensitivity analyses), point estimates or range estimates are used to assess the variability of results; usually the extreme values for each parameter are used and threshold values are determined at which the decision changes. These are one-way sensitivity analyses where one parameter is varied and all others remain constant. These often underestimate uncertainty. [633] The problem with deterministic analyses is that the extreme but plausible ranges are somewhat arbitrary, the probability of the extreme values is small, and therefore if the results are sensitive with these values, it makes interpretation difficult, any interaction between parameters is ignored and it is unclear how to estimate the probability of the threshold value occurring for any given parameter. [634]

Probabilistic sensitivity analyses will incorporate the probability distributions of variables; therefore, a distribution is specified for each parameter, and these distributions are sampled randomly which produces a distribution of the outcome. This is repeated to represent the possible range of values for the parameters. [635] The output gives the expected values for costs, effects and benefits as well as the probability that each alternative is cost-effective. [636] Distributions are chosen based on nature of the data, how the parameter is estimated and the research question. [637]

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[633] Claxton, "Exploring Uncertainty in Cost-Effectiveness Analysis."; Sun and Faunce, "Decision-analytical Modelling in Health-care Economic Evaluations."

[634] Andrew H. Briggs, "Handling Uncertainty in Cost-Effectiveness Models.," *PharmacoEconomics* 17, no. 5 (May 2000): 479–500; Claxton, "Exploring Uncertainty in Cost-Effectiveness Analysis."

[635] Sun and Faunce, "Decision-analytical Modelling in Health-care Economic Evaluations."

[636] Claxton, "Exploring Uncertainty in Cost-Effectiveness Analysis."

[637] Ibid.; Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.

Sensitivity analyses are important in the current study as the cost-effectiveness of a screening modality that is not currently used in the proposed setting is being compared to methods considered to be the "gold-standard." Estimates for heart failure incidence are low since older trials did not screen for this adverse effect; therefore, patients were only reported if they became symptomatic. Probabilistic sensitivity analyses will be performed for all variables. Beta distributions represent population values that are restricted to a range from zero to one, thus beta distributions were used for probabilities and utilities. Gamma distributions were used for cost variables as they are representative of skewed distributions.

4.6 Introduction to Utilities and HRQOL

Quality of life can be defined as "a state of complete physical, mental and social well-being, and not merely the absence of disease." [638] Since heart failure is a chronic condition for which there is no cure, the measurement or assessment of quality of life becomes important. Health-related quality-of-life is comprised of several components (which can also be referred to as domains or dimensions). Those include physical, psychological and social functioning, Figure 4.4 illustrates how these domains or dimensions contribute to the overall HRQOL. [639] Physical functioning may include how symptoms affect someone's daily life. Psychological functioning can be affected by depression from the realization of one's mortality or from impaired physical functioning. Social functioning includes decreased interaction with others which may be due to

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[638] Colin Berry and John McMurray, "A Review of Quality-of-Life Evaluations in Patients with Congestive Heart Failure.," *PharmacoEconomics* 16, no. 3 (1999): 247–271.
[639] Ibid.

symptoms, depression, inability to work due to recurrent hospitalizations, or physical limitations. [640] The decreased functioning with disease progression results in a decreased quality of life. Instruments are designed to measure both how treatment is improving the patients' well-being as well as the adverse effects of said treatment. [641] Quality of life can be measured either directly by obtaining responses from the patient, or indirectly by having the caregiver respond on the patients behalf or by obtaining the medical professional's assessment of the patient's quality of life. [642]

Figure 4.4 Domains of Health-Related Quality-of-Life[643]
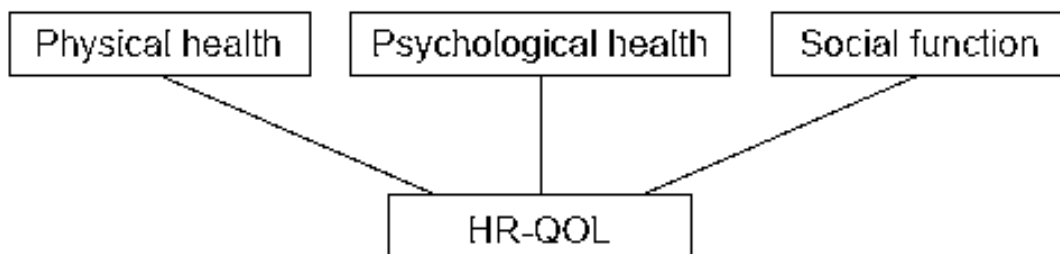
HR-QOL: Health-Related Quality-of-Life

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[640] Ibid.

[641] Ibid.

[642] Gordon H. Guyatt, David H. Feeny, and Donald L. Patrick, "Measuring Health-Related Quality of Life," *Annals of Internal Medicine* 118, no. 8 (April 15, 1993): 622 –629.

[643] Ibid.

4.6.1 QUALITY OF LIFE IN HEART FAILURE

There are numerous consequences of heart failure that can decrease a patient's quality of life such as physical, functional or social limitations as a result of the disease or due to the adverse effects of treatment. Figure 4.5 below illustrates a model of the quality of life in heart failure patients. There are many interacting factors in quality of life that can be affected for patients with heart failure. For example, symptoms can cause a limitation in the ability to perform activities of daily living (ADL), and increased symptoms can also affect mood, which can subsequently decrease willingness to perform certain activities. These interactions can therefore affect how quality of life is assessed in heart failure patients. For example, treatment that improves symptoms does not always lead to a corresponding improvement in reported quality of life. [644]

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[644] Thomas S. Rector, "A Conceptual Model of Quality of Life in Relation to Heart Failure," *Journal of Cardiac Failure* 11, no. 3 (April 2005): 173–176.

Figure 4.2 Conceptual Model of Quality of Life in Heart Failure[645]
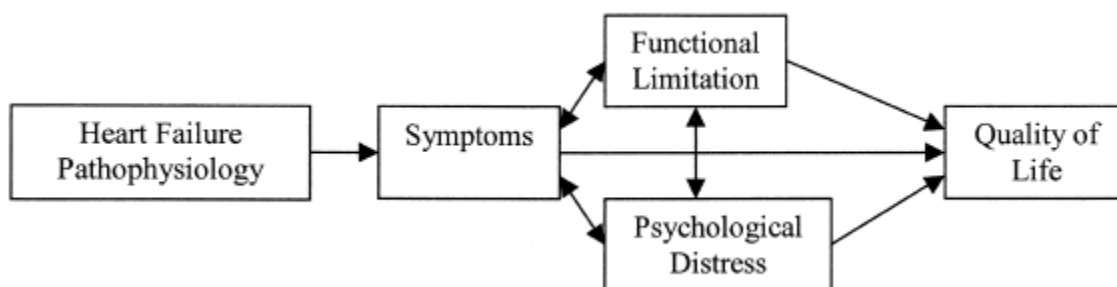
Quality-of-life in heart failure patients can be measured with both general instruments and disease-specific instruments. General instruments used include the Sickness Impact Profile (SIP), the 36- and 12-Item Short Form health surveys (SF-36 and SF-12), and the Quality of Well-Being Scale (QWB). Disease-specific instruments in heart failure include the Chronic Heart Failure Questionnaire, the Minnesota Living with Heart Failure Questionnaire (MLwHF), and the Quality-of-Life in Severe Heart Failure (QLQ-SFH).[646] Quality of life estimates, for the purposes of this study, were obtained from previously published literature, and for purposes of simplicity, patients are categorized as either symptomatic or asymptomatic.[647]

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[645] Ibid.

[646] Ibid.; Thomas S. Rector, Inder S. Anand, and Jay N. Cohn, "Relationships Between Clinical Assessments and Patients' Perceptions of the Effects of Heart Failure on Their Quality of Life," *Journal of Cardiac Failure* 12, no. 2 (March 2006): 87–92.

[647] Dennis G Fryback et al., "The Beaver Dam Health Outcomes Study Initial Catalog of Health-State Quality Factors," *Medical Decision Making* 13, no. 2 (June 1, 1993): 89–102.

4.7 Model Inputs

Estimates obtained for the model included the estimated number of patients expected to be included in the study population, incidence and prevalence estimates of heart failure, probability of correct diagnosis, probability of hospitalization and/or emergency department utilization, probability of symptomatic disease, probability of disease progression and expected mortality. Costs were obtained for the tests being compared, costs of treating discovered cardiac dysfunction (including medication cost, cardiology follow-up and medication management) and cost of potential hospitalization/emergency department utilization.

4.7.1 STUDY POPULATION

A hypothetical cohort of female patients diagnosed with invasive breast cancer and successfully treated (i.e., achieved complete remission) in the US during 2010 will be the population under study. SEER estimates that there will be 209,060 new cases diagnosed in 2010, including 54,010 *in situ* cases and 1,970 male cases. Since *in situ* cases are not treated with chemotherapy, these patients will not be exposed to the cardiotoxic treatment and therefore, will not be subject to further monitoring. Although male cases would be treated with the same chemotherapy regimens, cardiovascular outcomes would have to be modeled separately, thus they were also subtracted to reduce the model complexity. The resultant study population includes 153,080 patients. [648] All invasive cases are assumed to have received first-line therapy which includes the use of

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[648] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

anthracyclines. [649] The c-erb-B2 gene (or HER-2/neu) is overexpressed in 20-30% of invasive breast cancer cases; therefore, it is assumed that 25% (n = 30,616) will also receive trastuzumab, creating additional risk. Table 4.3 below summarizes the calculations used to determine the number of subjects in the hypothetical study population. [650]

Table 4.3 Summary of Study Population Calculation[651]

Study Population		
New cases - 2010	209,060	
New *in situ* cases	54,010	(55,980)
New male cases	1,970	
Total Study Population	209,060 - 55,980	153,080
Trastuzumab Cases	153,080 * 0.25	38,270
Anthracycline Cases	153,080 - 38,270	114,810

4.7.2 INCIDENCE OF HEART FAILURE

It has been shown that incidence of heart failure in breast cancer patients varies with the chemotherapy regimen received, and for anthracycline-based regimens, the cumulative dose. Other considerations included whether the patient received trastuzumab

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[649] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

[650] Abeloff et al., "Cancer of the Breast"; William Godolphin et al., "Studies of the HER-2-neu Proto-oncogene in Human Breast and Ovarian Cancer," *Science* 244 (1989): 707+; Hadi Yaziji et al., "HER-2 Testing in Breast Cancer Using Parallel Tissue-Based Methods," *JAMA: The Journal of the American Medical Association* 291, no. 16 (April 28, 2004): 1972 –1977.

[651] Howlader et al., "SEER Cancer Statistics Review 1975-2008."

with their chemotherapy regimen.[652] Limitations in using published heart failure incident data are that trials historically only report late-stage or symptomatic disease (NYHA Classes III and IV), so patients who had declining cardiac function, yet were without symptoms, would not have the disease detected during the trial.[653] Additionally, adverse effects are typically only recorded while the subjects are actively receiving the agent(s) under investigation and heart failure can develop up to 15 years after the completion of therapy. [654]

In a pooled analysis of seven phase II/III trials where 202 patient records were reviewed, 112 (55%) experienced some type of cardiac dysfunction and 62 (30.7%) met criteria for heart failure. However, of the seven trials, only one compared cardiac dysfunction in patients receiving the combination of doxorubicin and cyclophosphamide (rate of cardiac dysfunction = 8%) and those receiving that combination with trastuzumab (rate of cardiac dysfunction = 27%). [655] In a prospective evaluation of pediatric survivors of childhood cancer; patients that were treated with anthracyclines were subsequently monitored for up to 15 years. Lipschultz et al. found that 57% of children developed detectable cardiac dysfunction (Lipschultz et al. 1991). Frequently cited, dose-dependent

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[652] Jones, Swanton, and Ewer, "Anthracycline Cardiotoxicity"; Morandi et al., "Cardiac Toxicity of High-dose Chemotherapy"; Strevel and Siu, "Cardiovascular Toxicity of Molecularly Targeted Agents"; T. M. Suter, N. Cook-Bruns, and C. Barton, "Cardiotoxicity Associated with Trastuzumab (Herceptin) Therapy in the Treatment of Metastatic Breast Cancer," *The Breast* 13, no. 3 (2004): 173–183; Edward T. H. Yeh et al., "Cardiovascular Complications of Cancer Therapy," *Circulation* 109, no. 25 (June 29, 2004): 3122 – 3131; de Azambuja et al., "Cardiac Toxicity with anti-HER-2 Therapies: What Have We Learned so Far?".

[653] E. Bria et al., "Cardiotoxicity and Incidence of Brain Metastases After Adjuvant Trastuzumab for Early Breast Cancer: The Dark Side of the Moon? A Meta-analysis of the Randomized Trials," *Breast Cancer Research and Treatment* 109, no. 2 (2008): 231–239; S. M Ewer and M. S Ewer, "Cardiotoxicity Profile of Trastuzumab," *Drug Safety* 31, no. 6 (2008): 459–467; Suter, Cook-Bruns, and Barton, "Cardiotoxicity Associated with Trastuzumab (Herceptin) Therapy in the Treatment of Metastatic Breast Cancer."

[654] Steven E Lipshultz and Steven D Colan, "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer," *J Clin Oncol* 22, no. 5 (2004): 769–773; Lipshultz et al., "Late Cardiac Effects of Doxorubicin Therapy for Acute Lymphoblastic Leukemia in Childhood."

[655] Andrew Seidman et al., "Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience," *J Clin Oncol* 20, no. 5 (March 1, 2002): 1215–1221.

incidence rates of cardiac dysfunction are 3%, 7% and 18% for doses of 400, 550 and 700 mg/m^2, respectively. Other common and more recent incidence values are 5%, 26% and 48% for the same respective doses. Table 4.4 below summarizes incidence rates reported in trials of anthracycline regimens with and without trastuzumab and the corresponding citation. The studies in Table 4.4 give a range of incidence values of cardiac dysfunction of 0.6 to 57% (median = 15.4%) and 7 to 34% (median = 27%) for patients receiving anthracyclines and trastuzumab. The median values were the estimates used to calculate probabilities for each potential test outcome (Table 4.7).

Table 4.4 Incidence of Heart Failure Among Breast Cancer Patients Receiving Anthracyclines With and Without Trastuzumab

| Citation | Anthracycline Therapy | | With Trastuzumab | |
	C.D. (%)	H.F. (%)	C.D. (%)	H.F. (%)
Seidman, et al, 2002[1]	8	4	27	16
Piccart-Gebhart, et al. 2005	2.21	0.06	7.08	2.27
Suter, et al.[2]	NR	9.6	NR	28
Suter, et al. 2007[1]	NR	NR	7	0.6
Slamon, et al. 2005 [1]	0.6	1.2	2.4	2.3
Rastogi, et al. 2007[1]	NR	1.3	NR	4
Slamon, et al. 2001	8	3	27	16
Tan-Chiu, 2005	17	0.8	34	4.1
Gennari, et al. 1999[1]	20	9	NR	NR
Palmeri, et al. 2002[1]	15.4	NR	NR	NR
Erman, et al. 2005[1]	8	NR	NR	NR
LLuch, et al. 2000[1]	27.2	NR	NR	NR
Pagani, et al. 2000[1]	51	2	NR	NR
Venturini, et al. 1996[3]	11.25	3.75	NR	NR
Von Hoff, et al. 1979	NR	2.1	NR	NR
Swain, et al. 2000[3]	23.6	5.1	NR	NR
Lefrak, et al. 1973	NR	2.76	NR	NR
Lipshultz, et al. 1991	57	10	NR	NR
Shapiro, et al. 1998	8	6.8	NR	NR

C.D.: Cardiac Dysfunction; H.F.: Heart Failure; NR = Not Reported [1] Prospective Trial [2]Reporting Multiple Trials [3] Incidence in both arms, treatment arm received dexrazoxane

4.7.3 SENSITIVITY/SPECIFICITY OF EACH MONITORING TECHNIQUE

Test characteristics will be important to determine each test's ability to detect cardiac dysfunction prior to the development of symptoms. Characteristics under consideration include: sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and the diagnostic odds-ratio. Table 4.5 below describes the test characteristics for the various methods of screening for heart failure. The diagnostic odds-ratio (DOR) is a ratio of positivity in diseased divided by non-diseased patients and can be calculated using test characteristics such as the number of positive and negative test results, the test sensitivity and specificity, and positive and negative predictive values. [656]

$$DOR = \frac{(\frac{TP}{FN})}{(\frac{FP}{TN})} \qquad\qquad DOR = \frac{\left(\frac{PPV}{(1-PPV)}\right)}{\left(\frac{(1-NPV)}{NPV}\right)}$$

$$DOR = \frac{\left(\frac{Sensitivity}{(1-Sensitivity)}\right)}{\left(\frac{1-Specificity}{Specificity}\right)} \qquad\qquad DOR = \frac{PLR}{NLR}$$

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[656] Afina S. Glas et al., "The Diagnostic Odds Ratio: a Single Indicator of Test Performance," *Journal of Clinical Epidemiology* 56, no. 11 (November 2003): 1129–1135.

The positive likelihood ratio (PLR) is the ratio of detecting positive results in patients who have the disease in question over detection of positive results in healthy patients (i.e., patients who do not have the disease). A negative likelihood ratio (NLR) is the ratio of getting a negative result in patients who have the disease in question over healthy patients. [657] Positive and negative likelihood ratios are expressed as follows:

$$PLR = \frac{Sensitivity}{(1 - Specificity)} \qquad NLR = \frac{(1 - Sensitivity)}{Specificity}$$

Table 4.5 Comparison of Test Characteristics for Methods Under Comparison[658]

		Sensitivity	Specificity	DOR	PLR	NLR
	BNP[1]	0.93	0.74	39.50	3.57	0.09
Test	*ECHO[2]*	0.64	0.81	7.59	3.37	0.44
	MUGA	0.90	0.72	23.10	3.21	0.14

[1] Pooled results from 20 trials [2] Measured abnormal Fractional Shortening to predict either abnormal contractility or afterload in leukemia patients; DOR = Diagnostic Odds Ratio, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio

[657] Ibid.

[658] J Mant et al., "Systematic Review and Individual Patient Data Meta-analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic Strategies in Primary Care," *Health Technology Assessment (Winchester, England)* 13, no. 32 (July 2009): 1–207, iii; Lipshultz and Colan, "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer"; Nousiainen et al., "Concomitant Impairment of Left Ventricular Systolic and Diastolic Function During Doxorubicin Therapy."

Positive and negative predictive values are also related to test characteristics and are a function of the test's ability to obtain a positive (or negative) result in those patients who indeed have (or do not have) the disease in question. Table 4.6 below describes the relationship between test characteristics and positive/negative predictive values where TP=True Positives, FP= False Positives, FN=False Negatives, TN= True Negatives, PPV= Positive Predictive Value, NPV=Negative Predictive Value, and P= Prevalence [659]

Table 4.6 Calculation of the Number of Positive and Negative Results from Test Characteristics

		Disease or Target Disorder		
		(+)	(-)	
Test	(+)	TP	FP	$PPV = \dfrac{TP}{(TP + FP)}$
	(-)	FN	TN	$NPV = \dfrac{TN}{(TN + FN)}$
		$Sens. = \dfrac{TP}{(TP + FN)}$	$Spec. = \dfrac{TN}{(TN + FP)}$	$P = \dfrac{TP + FN}{TP + FP + FN + TN}$

(+) Denotes Positive Test/Disease Present; (-) Denotes Negative Test/Disease Absent; Sens.: Sensitivity; Spec.: Specificity

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[659] Glas et al., "The Diagnostic Odds Ratio: a Single Indicator of Test Performance."

The model input probabilities for test results for patients receiving anthracyclines only and regimens with the addition of trastuzumab are listed in Table 4.7 below. Probabilities were determined using the test characteristics listed in Table 4.6. The probability of diagnosis is 0.795; therefore, true positive results in the model are divided among patients that are diagnoses with and without symptoms. Those probabilities for both exposure types are listed in Table 4.8 below.

Table 4.7 Input Probabilities for Each Potential Test Result

Exposure Type	Test	TP	TN	FP	FN
Anthracyclines	BNP	0.143	0.626	0.220	0.011
	ECHO	0.099	0.685	0.161	0.055
	MUGA	0.139	0.609	0.237	0.015
Anthracyclines with Trastuzumab	BNP	0.251	0.540	0.190	0.019
	ECHO	0.173	0.591	0.139	0.097
	MUGA	0.243	0.526	0.204	0.027

Table 4.8 True Positive Inputs for Diagnosing HER-2 (+) and HER-2 (-) Patients as Asymptomatic

TEST	HER-2 (-)	HER-2 (+)
BNP	0.114	0.199
ECHO	0.079	0.138
MUGA	0.111	0.193

4.7.4 MORTALITY

There are several aspects that need to be considered with respect to mortality in this model. Patients may experience mortality from breast cancer, from heart failure, or from unrelated causes. Mortality estimates can vary by ACC/AHA stage and by age. Mortality from heart failure is reported a number of ways in the literature. One study found an annual mortality of 10 percent from heart failure (with 2.5 years of follow-up) regardless of clinical stage. [660] Multiple studies give mortality estimates in months or years from the index diagnosis of heart failure, while some report mortality by ACC/AHA stage or NYHA class. Additionally, some studies differentiate mortality in treated patients versus untreated patients, and those typically address specific treatment modalities. In Table 4.9 below, published estimates of five-year survival stratified by

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[660] John G.F. Cleland et al., "The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure," *N Engl J Med* 352, no. 15 (April 14, 2005): 1539–1549.

ACC/AHA stage [661] were taken and converted into the annual probability of death for patients in those respective stages.

Table 4.9 Annual Heart Failure Mortality Stratified By ACC/AHA Stage[662]

Stage	A 5-Year Survival	B 5-Year Mortality[1]	C Hazard Rate[2]	D Annual Probability[3]	Value Used
A	0.97	0.03	0.006091841	0.006073323	0.006
B	0.96	0.04	0.008164399	0.008131161	0.008
C	0.75	0.25	0.057536414	0.055912488	0.056
D	0.20	0.80	0.321887582	0.275220336	0.275

[1] Equals 1- Column A
[2] Hazard Rate= [-ln (1-column B)]/5
[3] $P(t) = 1 - \exp(-[\text{Column C}])$

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[661] Khawaja Afzal Ammar et al., "Prevalence and Prognostic Significance of Heart Failure Stages: Application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the Community.," *Circulation* 115, no. 12 (March 27, 2007): 1563–1570.
[662] Ibid.

4.7.5 COSTS

Only direct medical costs are considered relevant to the study as the perspective is that of the payer. Thus, lost wages, childcare, and transportation were not included. Indirect costs, such as decreased productivity, were also not included. The discount rate used was 3%.[663] Input costs considered for purposes of this study included the following: cost of the screening/monitoring test used plus cost of confirmatory testing; cost of heart failure treatment if discovered (i.e., medications and outpatient follow-up with appropriate specialists); and the cost of potential hospitalizations and/or emergency department visits.

4.7.5.1   Costs of Screening/Monitoring

The cost of screening/monitoring includes the cost of the test (the cost of specialized personnel for administering or interpreting test results are assumed to be included in Medicare reimbursement) and cost of confirmatory testing which for the purposes of this study will be assumed to be costs associated with an ECHO. Table 4.10 lists the 2010 Medicare reimbursement amounts for each test based on CPT code. Table 4.11 outlines some previously published costs for the screening methods under study.

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[663] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*; Gold et al., *Cost-effectiveness in Health and Medicine*.

Table 4.10 Medicare Reimbursement Associated With Monitoring

Test	CPT Code	Medicare Reimbursement ($)	OPPS ($)	Value Used ($)
BNP[1]	83880	47.77	N/A	48
ECHO	93306	265.07	522.12	393
MUGA	78472	269.90	357.30	361
	78481	231.63	358.77	
	78494	291.65	368.73	
	78496[2]	102.73	N/A	103
MUGA Total		373-395	461-472	*464

OPPS: Out-Patient Payment System – Maximum amount paid for a CPT code [1] CPT Code for Natriuretic Peptides, Reimbursement Amount from the Clinical Diagnostic Lab Fee Schedule; Descriptions [2] Code for add-on to procedure, * Used average of MUGA OPPS amounts plus add-on amount total MUGA Cost; See Appendix C for ECHO and MUGA Codes with Corresponding Medicare

Table 4.11 Other Published Costs for Screening/Monitoring Tests

Citation	Test	Cost ($)[1]	Year	2010 Cost ($)[2,3]
Tang, et al. [664]	BNP or NT-pro-BNP	50	2007	58
Nakamura, et al. [665]	BNP	32	2005	40
	ECHO	420	2005	526
Heidenreich et al. [666]	BNP	32	2001	48
	ECHO[4]	420	2001	625
Shureiqi et al. [667]	MUGA	781	1996	1,375
Dokainish et al. [668]	BNP	38	2004	50
	ECHO	338	2004	442

[1] Costs are reported in U.S. Dollars
[2] Costs realized at end of the 2010 calendar year
[3] Published Costs were standardized to 2010 using Medical CPI and rounded to the nearest dollar
[4] Cost for ECHO represented total reimbursement for CPT codes 93307, 93320 and 93325

4.7.5.2   Costs of Heart Failure Treatment

The cost of heart failure treatment includes the costs of optimal drug therapy for the corresponding heart failure stage, cardiology clinic follow-up, potential emergency department visits, and hospitalizations.   Table 4.12 below outlines interventions recommended for all or selected patients in the progressing stages of heart failure.   All patients in this hypothetical cohort begin in Stage A.   Treatment guidelines state that select patients in stage A could possibly be prescribed either an ACE-I or ARB. The population in this study is assumed to have no co-morbid conditions or contributing

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664 Tang et al., "National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure."

665 Motoyuki Nakamura et al., "B-Type Natriuretic Peptide Testing for Structural Heart Disease Screening: A General Population-Based Study," *Journal of Cardiac Failure* 11, no. 9 (December 2005): 705–712.

666 Heidenreich et al., "Cost-effectiveness of Screening with B-type Natriuretic Peptide to Identify Patients with Reduced Left Ventricular Ejection Fraction."

667 Shureiqi et al., "Clinical and Economic Impact of Multiple Gated Acquisition Scan Monitoring During Anthracycline Therapy."

668 Hisham Dokainish et al., "Comparative Cost-Effectiveness of B-Type Natriuretic Peptide and Echocardiography for Predicting Outcome in Patients With Congestive Heart Failure," *The American Journal of Cardiology* 97, no. 3 (February 1, 2006): 400–403.

factors adding to heart failure risk, thus it is assumed that patients in this hypothetical cohort have not been prescribed either agent; therefore cost of medications will only include those subsequent to the discovery of cardiac dysfunction as a result of monitoring.

Table 4.12 Medical Interventions Stratified by ACC/AHA Heart Failure Stage[669]

Stage	Routine Medication(s)	Medication(s) in Select Patients	Other Interventions
A		ACE-I (or ARB)	
B	ACE-I (or ARB) and β-Blocker		Implantable Defibrillator
C	Diuretics, ACE-I or ARB, Beta- Blocker	Aldosterone Antagonist, Digitalis, Hydralazine/Nitrate	Biventricular Pacing Implantable Defibrillator
D			Heart Transplantation Chronic Inotropes Permanent mechanical support, Hospice

ACE-I: Ace-Inhibitor, ARB: Angiotensin-Receptor Blocker, β-Blocker: Beta-Blocker

4.7.5.2.1   Medications

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[669] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

The costs of medications, for purposes of this study, are the costs for the optimal treatment for each corresponding heart failure stage. For simplicity, one representative agent was selected from each guideline-recommended class of medications prescribed at each heart failure stage. Representative medications from each class of medications used for treatment will be as follows: angiotensin-converting enzyme inhibitor = lisinopril; angiotensin-receptor blocker = losartan; beta-blocker = carvedilol; aldosterone inhibitor = spironolactone. Additionally, costs were obtained for medications frequently used for symptom control, including the following drug classes and medications: loop diuretic = furosemide; nitrate = isosorbide dinitrate (ISDN); and vasodilators = hydralazine. Lisinopril was chosen since it is the most commonly prescribed ACE-I and losartan was chosen since it is the only ARB currently available as a generic. Beta-blockers that have been shown to reverse remodeling in heart failure include metoprolol, carvedilol and bisoprolol. Both metoprolol and bisoprolol have high selectivity for the beta-1 receptor, where carvedilol blocks the beta-1, beta-2 and alpha-1 receptors. [670] Studies have suggested that the slight difference in mechanism improves mortality as well as more profound improvements in ejection fraction and NYHA class, therefore, carvedilol was chosen as the representative beta-blocker used in this study. [671]

All medications are available in a generic formulation and costs were obtained from the Texas Medicaid website; the median maximum allowable charge (MAC) value

[670] Michael R. Bristow et al., "Selective Versus Nonselective B-blockade for Heart Failure Therapy: Are There Lessons to Be Learned from the COMET Trial?," *Journal of Cardiac Failure* 9, no. 6 (December 2003): 444–453.

[671] Philip A Poole-Wilson et al., "Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised Controlled Trial," *The Lancet* 362, no. 9377 (July 5, 2003): 7–13; Farzan S. Rajput et al., "Choosing Metoprolol or Carvedilol in Heart Failure (a pre-COMET Commentary)," *The American Journal of Cardiology* 92, no. 2 (July 15, 2003): 218–221; John E Sanderson et al., "Beta-blockade in Heart Failure: A Comparison of Carvedilol with Metoprolol," *Journal of the American College of Cardiology* 34, no. 5 (November 1, 1999): 1522–1528.

was used. For medications that have been shown to improve heart failure survival and reverse remodeling (i.e., ACE-I, ARB, β-Blocker, aldosterone inhibitors), estimates used were those representing the target daily dose. For medications prescribed to improve symptoms, such as nitrates and diuretics, the estimates were obtained for the most commonly prescribed regimens.

For purposes of this study, the input costs for heart failure medication treatment was the total annual calculated cost of medication for either asymptomatic (B) or symptomatic (C/D) cardiac dysfunction. Asymptomatic patients in stage B were assumed to receive optimal drug therapy as recommended by the ACC/AHA guideline, which includes the use of either an ACE-I or ARB in addition to a beta-blocker.[672] Drug therapy for symptomatic patients includes medications used for stage B, plus the addition of an aldosterone inhibitor (spironolactone) and medications prescribed for the management of symptoms, which includes the use of nitrates, vasodilators and diuretics. Patients who were initially prescribed an ACE-I instead of an ARB, may have an ARB added at this point. It will be assumed that symptomatic patients will be prescribed furosemide, plus ISDN and hydralazine. Tables 4.13 and 4.14 illustrate the annual costs of the selected representative agents and the total costs for treating asymptomatic and symptomatic stages.

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[672] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

Table 4.13 Drug Therapies Included in Heart Failure Regimens and Their Respective Costs

Drug Class	Representative Agent[1]	Dose (mg)[2]	Unit Cost ($)[3]	Daily Cost	Annual ($)[4]
ACE-I	Lisinopril	40	0.124	0.124	44.64
ARB	Losartan	100	0.683	0.683	245.88
B-Blocker	Carvedilol	25[5]	0.112	0.448	161.28
Aldosterone Inhibitor	Spironolactone	50	0.477	0.477	171.72
Diuretic	Furosemide	40[6]	0.43	0.86	309.60
Nitrate	Isosorbide Dinitrate	20[7]	0.042	0.252	90.72
Vasodilator	Hydralazine	150[7]	0.242	0.726	261.36

[1] Representative Agents are drugs selected from each drug class to determine medication costs used in current study

[2] Dose is the upper limit of target or usual dose in mg per day

[3] Costs per-unit for generic medications are MAC for TX Medicaid

[4] Annual cost based on cost of 30-day supply for 12 months

[5] Largest tablet strength is 25mg; therefore dose estimation is two tablets twice daily

[6] Furosemide dose range is 20-160mg daily, 40 mg twice daily used for estimation

[7] Isosorbide dinitrate is available is 20mg tabs, dose is 40mg TID; Hydralazine dose range is 25-100mg TID, used 50mg three times daily for estimation

Table 4.14 Annual Estimated Cost of Heart Failure Medications by Stage

Stage	Cost per Year		Value Used
	Low[1]	High[1]	
B[2]	206	407	226[3]
C/D[4]	1039	1285[5]	1162

[1] Amount rounded to nearest dollar

[2] Includes ACE-I *or* ARB, and Beta-Blocker

[3] Reflects that 10% of patients will likely need to switch to an ARB from ACE-I as a result of adverse effects

[4] Includes medications for stage B plus spironolactone, furosemide and ISDN + hydralazine

[5] Includes the addition of ARB to ACE-I

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4.7.5.3   Additional Costs of Heart Failure Management

Since heart failure is a chronic condition, long-term management often involves frequent hospitalizations and/or emergency department visits, continual monitoring of cardiac function and office visits with a medical specialist. Patients may also receive outpatient medication management by a pharmacist, nurse practitioner or physician's assistant. Previously published costs with ranges that are relevant to the present study are outlined in Table 4.14; reported costs are adjusted to 2010 for comparison.

Table 4.15 Previously Published Costs of Heart Failure Treatment

Intervention	Cost ($)	Range ($)	Year	2010 ($)[1]
Lisinopril[2]	226	200-600	2001	336
Carvedilol[2]	1,152	89-1,300	2001	1,715
Outpatient Management[2]	1,700	500-3,000	2001	2,531
Additional Testing[2]	2,200	0-3000	2001	3,275
Hospitalization[2]	5,574	4000-10,000	2001	8,298
Hospitalization[3]	5,501	NR	1997	9,360
Hospitalization[4]	5,376	NR	2005	6,730

NR = Not Reported; [1]Costs standardized to 2010 using Medical CPI and Rounded to Nearest Dollar; [2] Heidenreich et al. [673] ; [3]Jessup et al.[674] ; [4] Hauptman et al. [675]

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[673] Heidenreich et al., "Cost-effectiveness of Screening with B-type Natriuretic Peptide to Identify Patients with Reduced Left Ventricular Ejection Fraction."

[674] Mariell Jessup and Susan Brozena, "Heart Failure," *The New England Journal of Medicine* 348, no. 20 (May 15, 2003): 2007–2018.

[675] Paul J. Hauptman et al., "Resource Utilization in Patients Hospitalized with Heart Failure: Insights from a Contemporary National Hospital Database," *American Heart Journal* 155, no. 6 (June 2008): 978–985.e1.

The cost for heart failure hospitalization was obtained from the Medicare reimbursement amount for heart failure Medicare-Severity Diagnosis-Related Group (MS-DRG) discharge codes (291, 292 and 293). Available estimates for 2009 are listed in Table 4.16 and adjusted to 2010. The costs of emergency department (ED) visits were estimated by obtaining the Medicare facility limiting charge for the corresponding Medicare HCPCS codes (99283, 99284, and 99285). The costs of each respective HCPCS code are listed in Table 4.17.

Table 4.16 Average Reimbursement for Heart Failure Medicare Severity – Diagnosis-Related Groups (MS-DRG)

MS-DRG	Description	Average Payment (2009)[1]	2010 ($)[1,2]
291	HF & Shock w/ MCC	9,005	9,609
292	HF & Shock w/ CC	5,794	6,183
293	HF & Shock	3,969	4,235
Averages:		**6,256**	**6,676**

LOS: Length of Stay, MCC: Major Complication/Comorbidity, CC: Complication/Comorbidity
[1] Medicare Payments in U.S. Dollars [2] Rounded to Nearest Dollar

Table 4.17 CMS Reimbursement for Emergency Department Visits in 2010

HCPCS Code	Description	National Payment Amount [1,2]
99283	ED Visit	68
99284	ED Visit	130
99285	ED Visit	191
Average:		**130**

[1]2010 Facility-Limiting Charges from CMS Website; [2]Rounded to Nearest Dollar

The costs of office visits were determined using Medicare CPT Codes including the cost of care for new patients as well as established patients. It was assumed that patients would incur the cost for new patients once; the value used was the average charge for CPT codes 99203 and 99204. For established patients, the value used was the average of charges for CPT codes 99212, 99213, 99214 and 99215. The frequency of follow-up depends on stage of disease progression. Since guidelines for management do not specify a specific frequency of surveillance, it was assumed that patients in stage B disease would follow-up twice annually, those in stages C/D would follow-up quarterly. Additionally, the frequency of medication management would also vary depending on disease stage. It was assumed that patients in Stage B would incur these charges quarterly; Stages C/D would incur charges monthly. These are listed in Table 4.18.

Table 4.18 Cost Estimates for Heart Failure Outpatient Management

Code	Description	Reimbursement ($)	Value Used[1]
99203	Office/Outpatient Visit, New	81.37	110
99204	Office/Outpatient Visit, New	137.77	
99212	Office/Outpatient Visit, Est.	27.39	
99213	Office/Outpatient Visit, Est.	53.98	70
99214	Office/Outpatient Visit, Est.	82.98	
99215	Office/Outpatient Visit, Est.	117.23	
90862	Medication Management	62.84	63

[1] Rounded to the Nearest Dollar; Est.: Established Patient

Table 4.19 Total Outpatient Management Costs by Stage

		Stage B		Stages C/D	
Intervention	*Unit Cost ($)*	*Frequency*	*Annual Amount ($)*	*Frequency*	*Annual Amount ($)*
O.V.	70	2	140	4	280
M.M.	63	4	252	12	756
Meds			226		1,162
Total			618		2,198

O.V.: Office Visits; M.M.: Medication Management; Meds: Medications

4.7.6 ADDITIONAL RELEVANT PROBABILITIES

Other relevant considerations include the discount rate, probability patients will be diagnosed without symptoms, probabilities for disease progression, probability of patients seeking acute care, and utility estimates. The discount rate used was 3%.[676] The reported range of breast cancer patients testing positive for HER-2 overexpression is 20 – 30%; therefore, 25% was chosen for use in this study. [677]

To determine the probability of heart failure severity on diagnosis several calculations had to be made. First, an estimation of the incidence of diastolic vs. systolic heart failure on diagnosis is required. A recent review by McMurray estimates that 50% of patients will be diagnosed with either diastolic or systolic dysfunction. [678] Then, an estimation of the probability of symptomatic disease in each systolic and diastolic dysfunction was necessary. In systolic dysfunction, McDonagh estimates that 77% of patients will present with asymptomatic dysfunction. [679] While it is estimated that 82% of patients with diastolic dysfunction will present with asymptomatic disease. [680] These estimates yield a probability of diagnosis with asymptomatic of 0.795. The probability of progression of heart failure is dependent upon whether the patient is being treated appropriately. For patients receiving treatment, the annual probability of progressing from asymptomatic to symptomatic dysfunction is 0.065. For those patients with

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[676] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.

[677] Abeloff et al., "Cancer of the Breast."

[678] John J. V McMurray, "Systolic Heart Failure," *N Engl J Med* 362, no. 3 (2010): 228–238.

[679] T A McDonagh et al., "Biochemical Detection of Left-ventricular Systolic Dysfunction," *Lancet* 351, no. 9095 (January 3, 1998): 9–13.

[680] Richard J. Rodeheffer, "Measuring Plasma B-type Natriuretic Peptide in Heart Failure: Good to Go in 2004?," *Journal of the American College of Cardiology* 44, no. 4 (2004): 740–749.

asymptomatic dysfunction that are not receiving medical treatment, the annual probability of disease progression is 0.098. [681]

Additional health states for the model include two levels of acute care; hospitalizations and emergency department visits. The probability of hospitalization depends on if patients have a history of heart failure symptoms. The probability of hospitalization for symptomatic patients has been previously published; the estimate for asymptomatic patients was obtained from subtracting that estimate from a published estimate for annual probability of hospitalization for all heart failure patients, which was 0.209.[682] Therefore, the annual probabilities of hospitalization are 0.11 and 0.099 for symptomatic and asymptomatic patients, respectively. The annual probability of an emergency department visit is 0.042.[683]

Once patients have been hospitalized for heart failure, there is a high probability of readmission, especially within the first thirty days after discharge. Estimates of re-hospitalization rates vary widely in the published literature ranging between 20 to 40%. Published rates typically depend on the length and type of follow-up after discharge. In the present study, an annual probability estimate of 0.33 was used for re-hospitalization and it is assumed this rate corresponds to the cycle length of one year.[684] In addition to high readmission rates after an index admission, but the risk of mortality immediately following discharge increases substantially. Like the rates of re-hospitalization, post-discharge mortality has a wide range of published estimates, often depending on the

[681] Heidenreich et al., "Cost-effectiveness of Screening with B-type Natriuretic Peptide to Identify Patients with Reduced Left Ventricular Ejection Fraction."

[682] Ibid.; J Mackowiak, "Cost of Heart Failure to the Healthcare System," *The American Journal of Managed Care* 4, no. 6 Suppl (June 1998): S338–342.

[683] Mackowiak, "Cost of Heart Failure to the Healthcare System."

[684] John J McMurray and Simon Stewart, "Epidemiology, Aetiology, and Prognosis of Heart Failure," *Heart* 83, no. 5 (2000): 596–602.

length and type of follow-up. In the present study, the post-discharge mortality estimate was 0.22. [685] Additionally, for all patients that are hospitalized, there is a risk of mortality associated with while being treated as an in-patient. The estimate used for mortality associated with hospitalization is 0.061.[686]

The utility estimates considered were that of various heart failure stages, disutility for additional testing required, and the utility associated with hospitalization. There are baseline assumptions made such that patients do not have a past medical history or additional risk factors for the development of heart failure and their cancer has been treated to complete remission, essentially eliminating consideration of co-morbid conditions. Thus, as all patients enter the model in Stage A, the utility estimate for all patients at baseline is 1.0. Heart failure progression to Stage B or Stages C/D has utility estimates of 0.865 and 0.710 respectively, and hospital admission has a utility estimate of 0.57. [687] Table 4.18 is a comprehensive list of additional relevant probability estimates and model inputs.

[685] Laura R. Loehr et al., "Heart Failure Incidence and Survival (from the Atherosclerosis Risk in Communities Study)," *The American Journal of Cardiology* 101, no. 7 (April 1, 2008): 1016–1022.
[686] Carisi A. Polanczyk et al., "Ten-Year Trends in Hospital Care for Congestive Heart Failure: Improved Outcomes and Increased Use of Resources," *Arch Intern Med* 160, no. 3 (February 14, 2000): 325–332.
[687] Fryback et al., "The Beaver Dam Health Outcomes Study Initial Catalog of Health-State Quality Factors"; Graham Nichol et al., "Cost-Effectiveness of Cardiac Resynchronization Therapy in Patients with Symptomatic Heart Failure," *Annals of Internal Medicine* 141, no. 5 (September 7, 2004): 343–351.

Table 4.20 Additional Relevant Probabilities

Citation	Parameter	Model Input
Drummond, et al. 2005; Gold, et al. 1996	Discount Rate	0.030
Abeloff, et al. 2008	HER-2 Positive	0.250
HF Type on Diagnosis		
	Stage B (ASX) on Diagnosis	0.795
Quality of Life Weights		
Assumption	Stage A	1.000
Fryback, et al. 1993	Stage B	0.865
	Stages C/D	0.710
Nichol, et al. 2004	Hospitalization	0.570
SF-6D	Disutility Associated with Each ECHO or MUGA Scan	0.025
Mortality		
Loehr, et al. 2008	1-Year Mortality after Hospitalization	0.220
Polanczyk, 2000	In- Hospital Mortality	0.061
HF Stage Progression		
Heidenreich, et al. 2004	ASX (B) to SX (C or D) (With TX)	0.065
	ASX (B) to SX (C or D) (Without TX)	0.098
Acute Care States		
Hospitalizations		
Heidenreich, et al. 2004	Hospitalization – SX Patients	0.110
Mackowiak, 1998	HF-Hospitalizations- All Patients	0.209
Hospitalizations for All Pts. – SX Pts.	HF- Hospitalizations –ASX Patients	0.099
McMurray and Stewart, 2000	Probability of Readmission [4]	0.330
Emergency Department Visit		
Mackowiak, 1998	HF-ED Visits – All Patients	0.042

[1] Median medication compliance value from 19 studies reviewed

[4] Readmission within one year

ASX = Asymptomatic, SX = Symptomatic, TX = Treated appropriately

4.7.7 ADDITIONAL MODEL CONSIDERATIONS

4.7.7.1   Cycle Length/Termination Condition

The Markov model will simulate the duration and frequency of the expected follow-up/surveillance of breast cancer patients that is recommended by NCCN and ASCO. Each cycle will be a calendar year, monitoring will occur quarterly for the first three years, every six months for the following two years, then annually thereafter. [688]

4.7.7.2   Proposed Model Structure

This section will provide a detailed structure of the proposed model to assess the cost-effectiveness of using BNP to monitor breast cancer patients compared to current standards. The decision node gives the choice between using BNP, ECHO or MUGA as the method of monitoring or the option of doing nothing. Figure 4.6 illustrates the tree structure for the decision node with the available alternatives. The Markov node from each testing modality and HER-2 status can result in either true negative, false positive, false negative, diagnosed asymptomatic, or diagnosed symptomatic as shown in Figure 4.7. The potential transitions included in the model are represented in the state-transition diagram for heart failure in Figure 4.8 and are depicted in tree structure in Figures 4.9 – 4.13. Patients can remain in Stage A (asymptomatic, normal heart structure/ejection fraction), transition to Stage B (asymptomatic, change in heart structure or decreased ejection fraction), transition to Stages C/D (symptomatic) or reach the absorbing stage (i.e., death). Additional transition states will be included to represent hospitalizations and

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[688] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

emergency department visits. Probabilities of each outcome were obtained from published literature.

Figure 4.6 Tree Structure for Monitoring Decision Node

No Monitoring

MUGA — HER(+) / p_HER2 / HER(-) #

ECHO — HER(+) / p_HER2 / HER(-) #

BNP — HER(+) / p_HER2 / HER(-) # 3

Monitoring For...
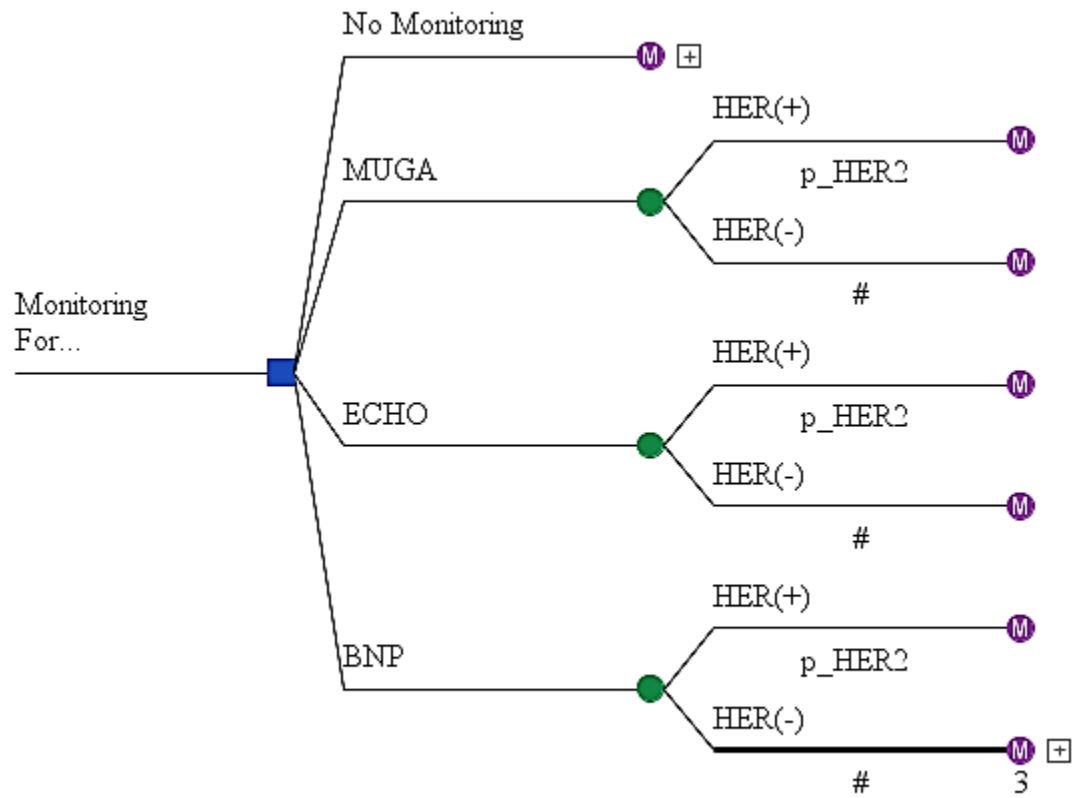
Figure 4.7 Tree Structure for Each Markov Node Associated With Testing
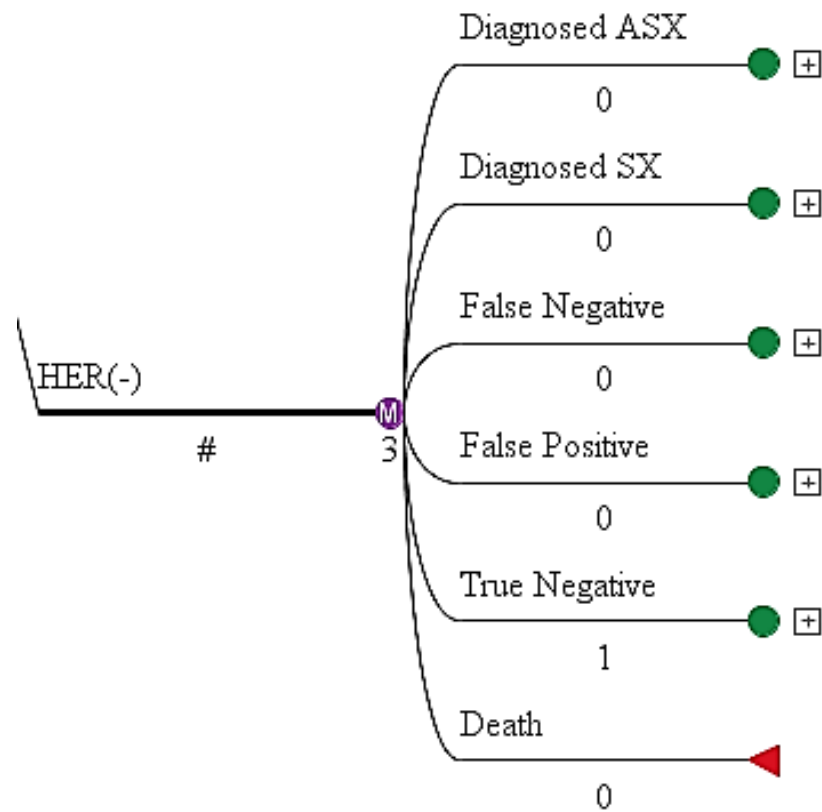
Figure 4.8 Illustration of Heart Failure Disease State Transitions

*Model Entry
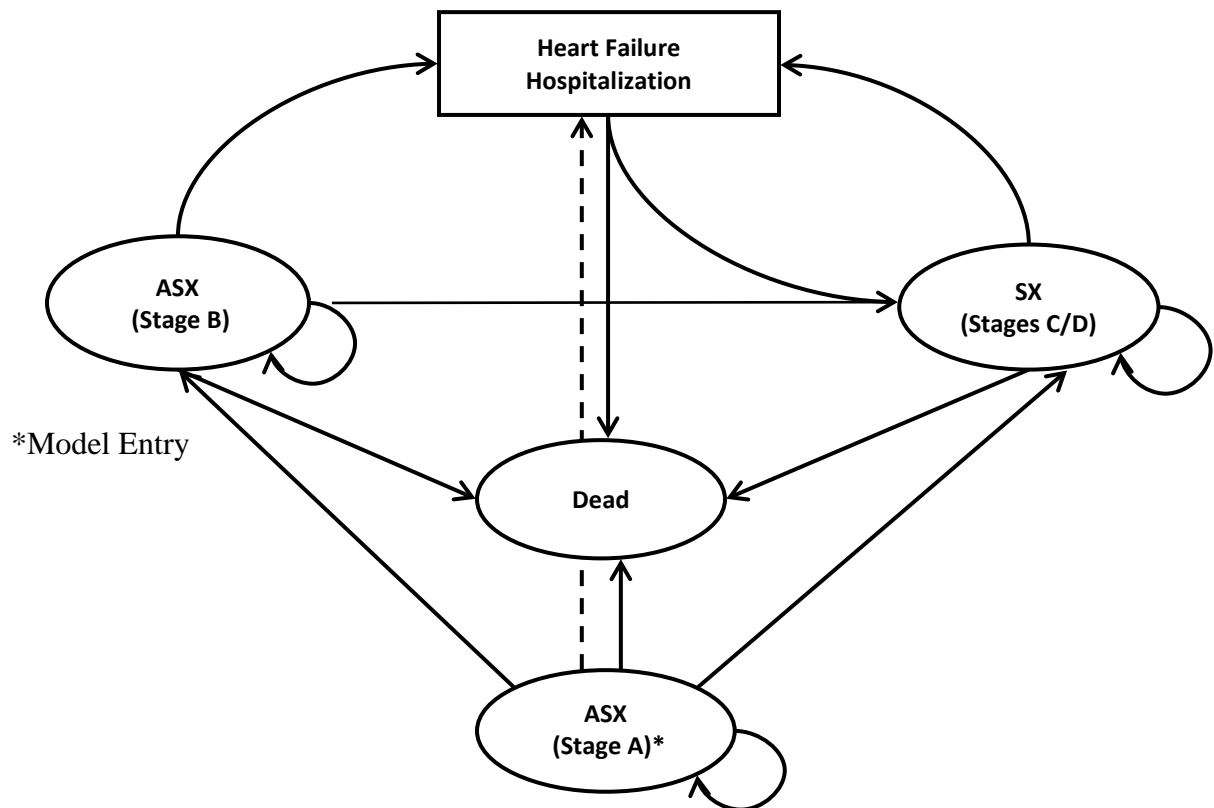
Figure 4.9 Tree Structure for "Diagnosed Asymptomatic" Branch
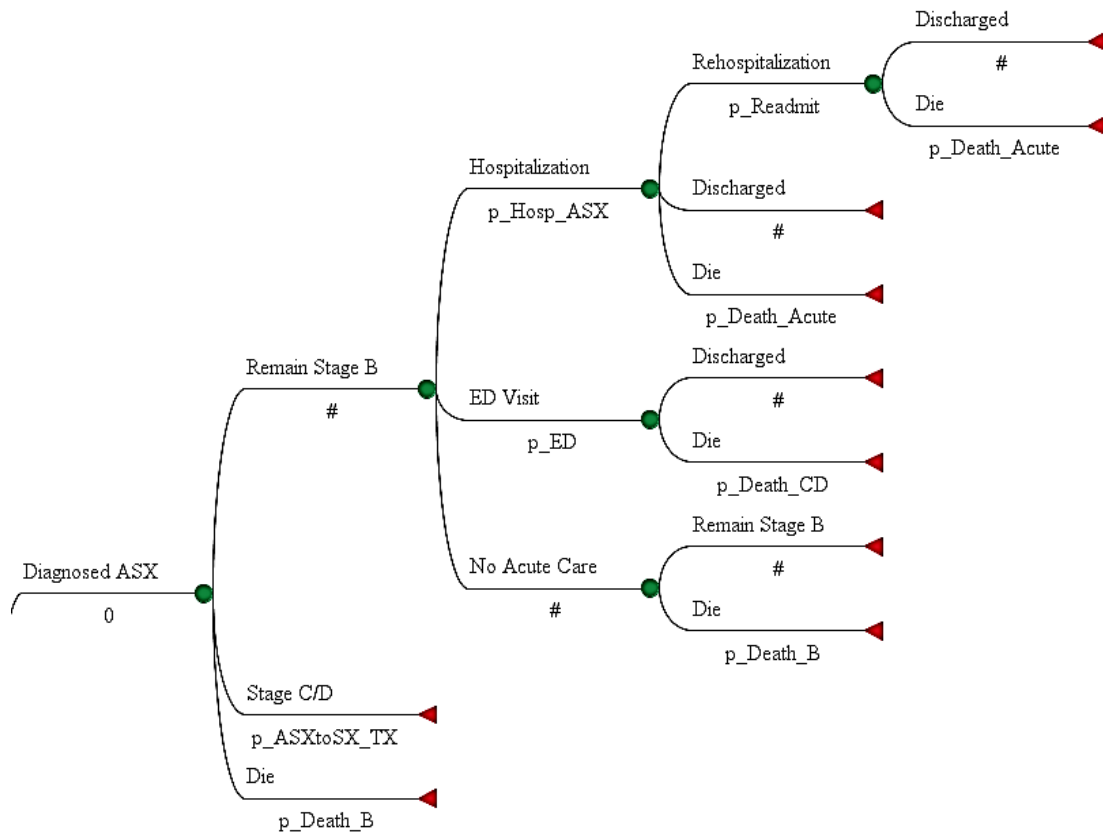
Figure 4.10 Tree Structure for "Diagnosed Symptomatic" Branch
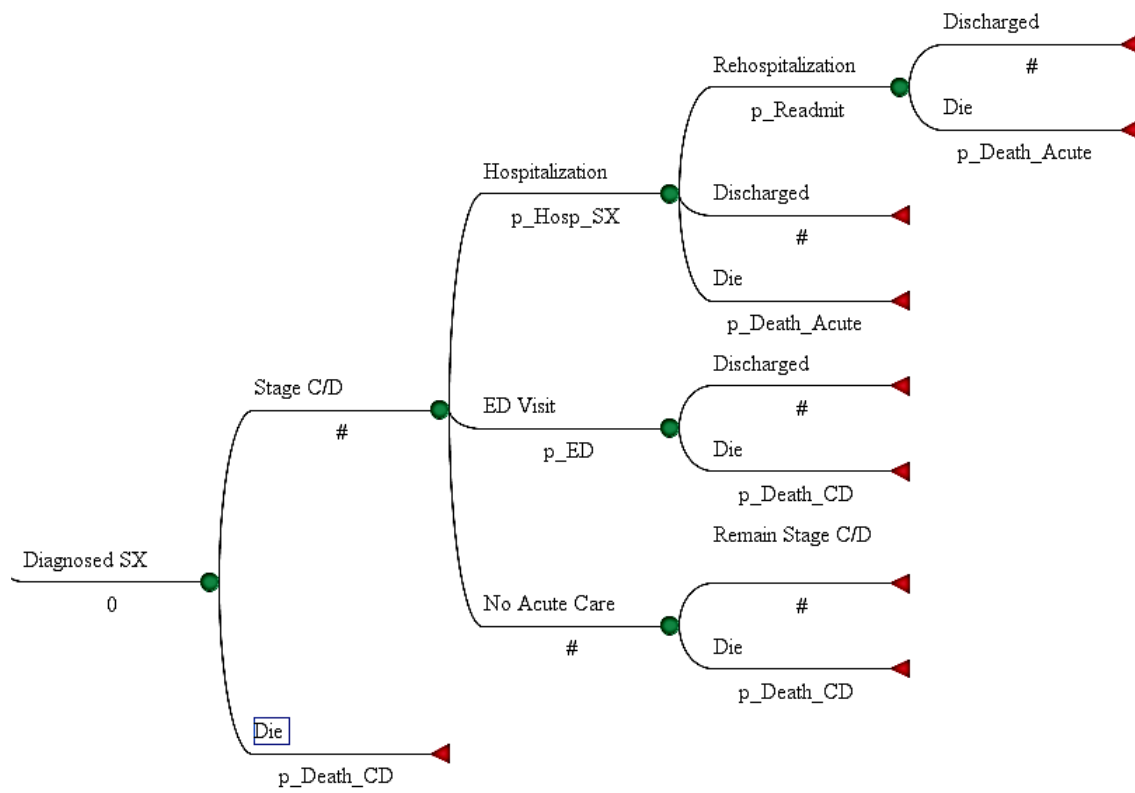
Figure 4.11 Tree Structure for False Negative (FN) Branch
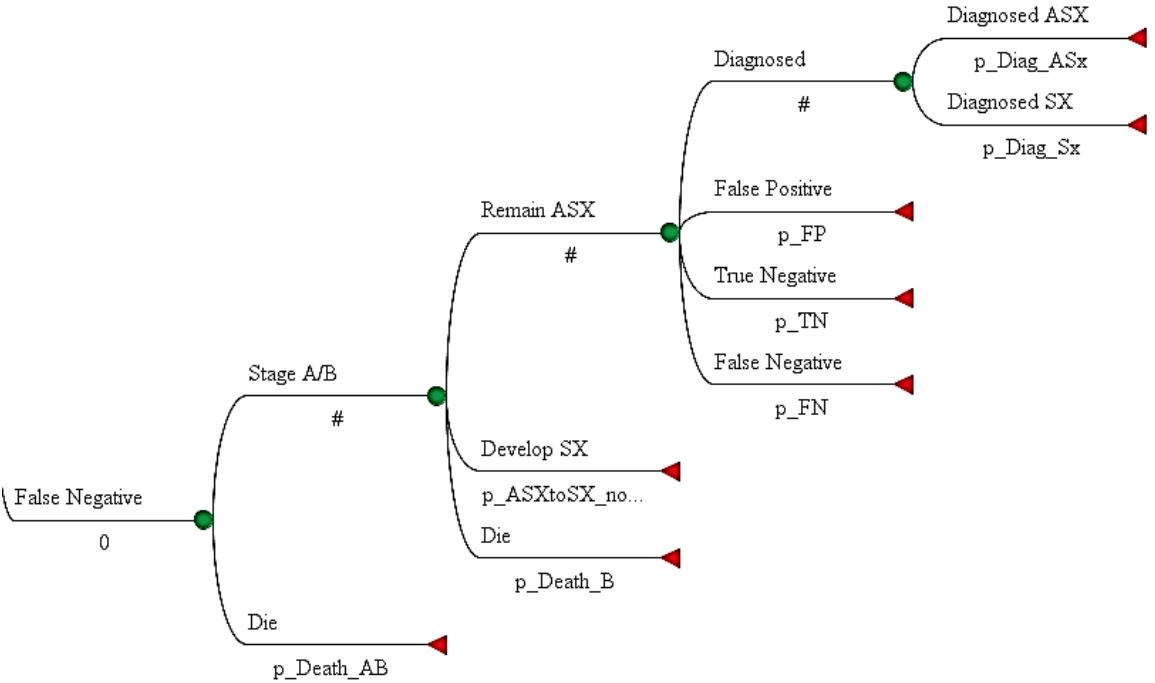
Figure 4.12 Tree Structure for False Positive (FP) Branch
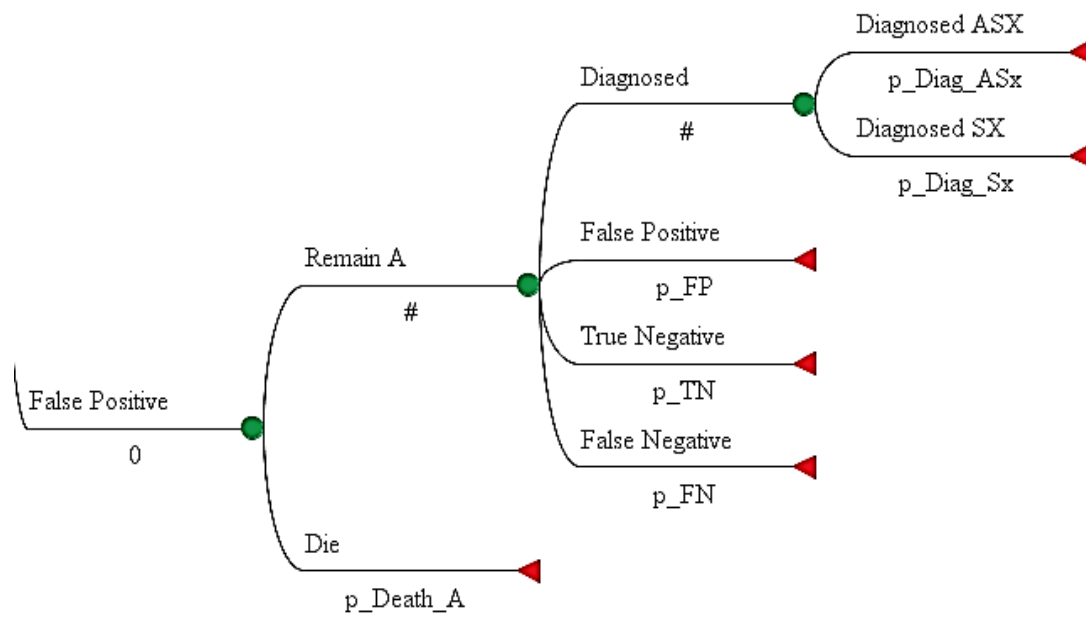
Figure 4.13 Tree Structure for True Negative (TN) Branch
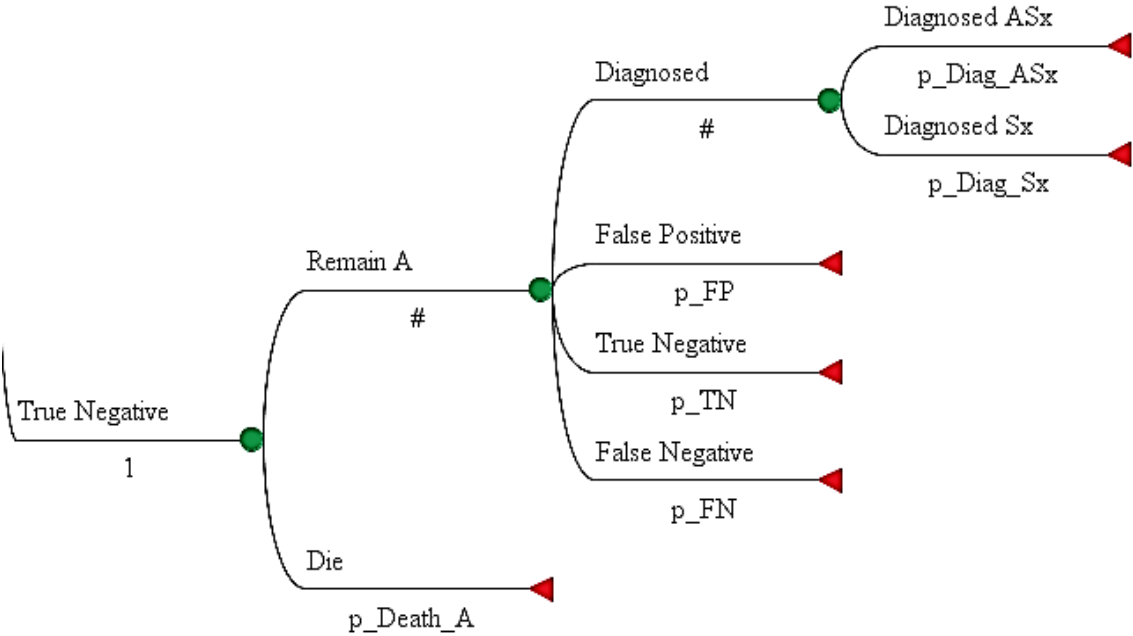
Figure 4.14 Tree Structure for the "No Monitoring" Branch
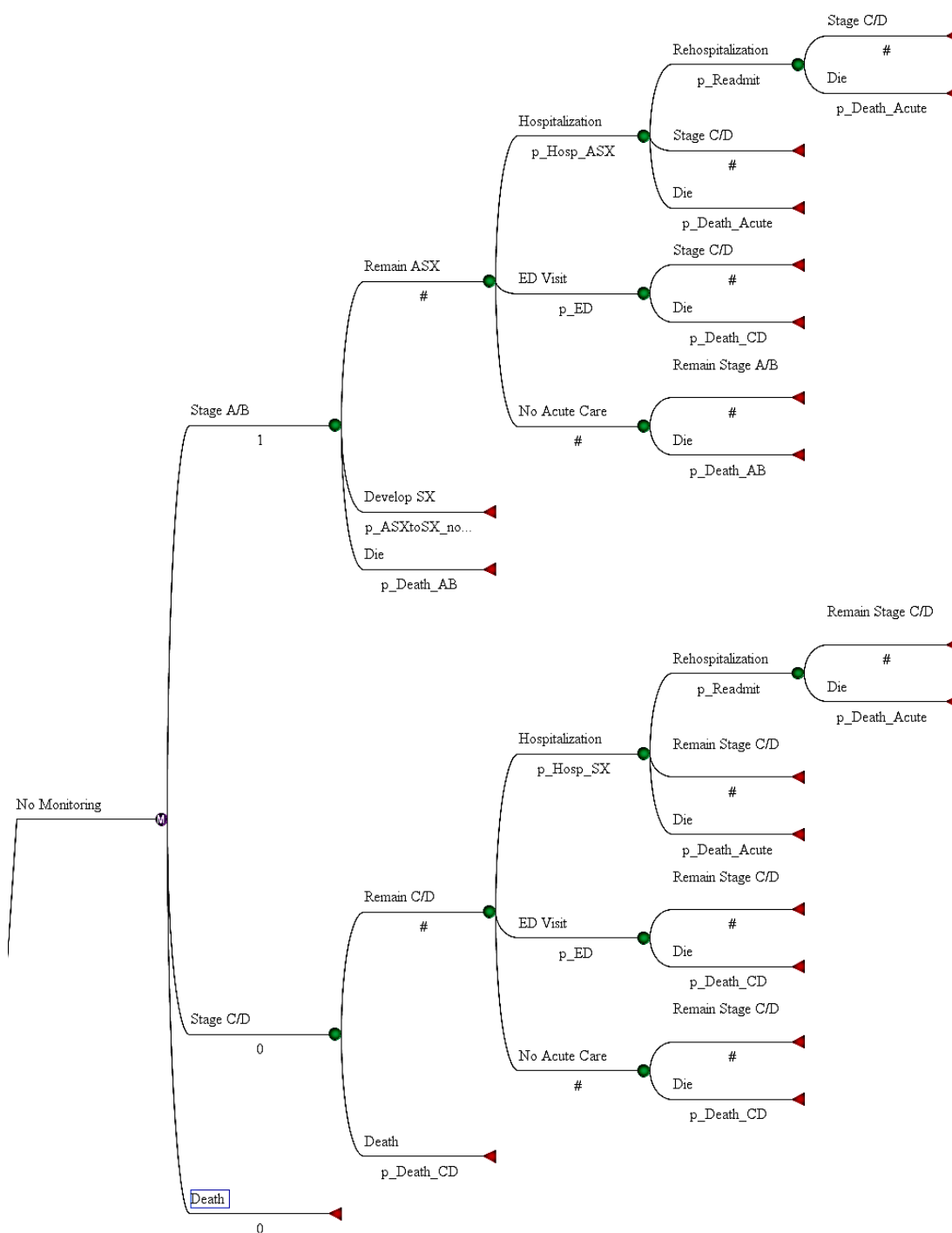
4.7.8 MODEL ASSUMPTIONS

- All patients were diagnosed with invasive-type breast cancer, were treated successfully (i.e., to complete remission with treatment concluded)

- Since the premise of the study is that all patients have been exposed to potentially cardiotoxic therapy, all patients begin in ACC/AHA Class A – however, since patients in the cohort are assumed to have no other risk factors for cardiac dysfunction above the exposure to the cardiotoxic agents under study, the patients enter the model without prior treatment with ACE-I or β- blockers

- All invasive breast cancer patients have been treated with an anthracycline-based chemotherapy regimen, and patients testing HER-2 positive will have been treated with trastuzumab

- Patients cannot transition backwards once they transition to a particular state

- All patients will undergo the appropriate recommended surveillance upon completion of therapy

- Each test is to be performed at follow-up intervals recommended by ASCO and NCCN

- Patients with an abnormal BNP finding will have a confirmatory test utilizing ECHO

- False positive results from BNP will yield the correct result with confirmatory testing

- All patients with a diagnosis of heart failure will be prescribed the appropriate therapy as recommended by ACC/AHA guidelines for the corresponding stage of disease

- The discount rate is 3% for costs, effectiveness, and utilities

- Disutility for each additional appointment associated with ECHO/MUGA = 0.025

- Patients cycling through the "No Monitoring" strategy that develop symptoms consistent with heart failure, will be treated appropriately

4.8 Summary of Chapter Four:

The perspective of the payer was chosen for the analysis; therefore, only direct costs are considered. Markov modeling was chosen over decision analysis since it was deemed important to represent the several stages of heart failure patients could potentially experience as well as varying mortality based on the stage the patient resides. Benefits of this study are represented by QALYs since heart failure is a chronic condition and there are numerous consequences of heart failure that can affect quality of life as well as length of life. It was decided to run the model over 15 years since there are reports of heart failure being diagnosed in exposed patients up to 15 years after treatment has concluded. The model will be analyzed using TreeAge Pro 2012® (TreeAge Software Inc., Williamstown, MA). Probabilistic sensitivity analyses will be conducted for all variables using beta distributions for both probabilities and utilities, and gamma distributions for costs. The results of the analysis will be presented in the next chapter.

CHAPTER FIVE: RESULTS

5.1   Introduction

This chapter includes the results for each of the study objectives, information on strategies under comparison, incidence of treatment-induced cardiac dysfunction, cost of monitoring, costs of outpatient heart failure treatment, and costs of acute care. The detailed results of cost-effectiveness analysis and sensitivity analyses are also included in this chapter. Results are divided into two sections by testable and non-testable hypotheses.

5.2   Objectives

5.2.1   OBJECTIVES WITHOUT TESTABLE HYPOTHESES

5.2.1.1 Objective One

Objective one was to describe each strategy under comparison in the current study. Many options exist for the monitoring of cardiac dysfunction after chemotherapy. These include invasive methods such as biopsies, radiological methods such as echocardiography and multi-gated acquisition scanning. In this study there are three monitoring alternatives being compared which include natriuretic peptides, ECHO and MUGA, as well as the option of doing nothing. Natriuretic peptides (BNP or NT-pro-BNP) levels are estimated quantitatively from a blood sample that could be added to routine labs obtained during scheduled breast cancer surveillance. Both BNP and NT-pro-BNP are measured in pg/mL in U.S. assays. The suggested normal range is 0.5 – 30

pg/mL (0.15 – 8.7 pmol/L) for BNP and 68-112 pg/ml (8.2 – 13.3 pmol/L) for NT-pro-BNP. The suggested cut-off point for the detection of heart failure is 100 pg / mL. [689]

Radiological procedures used for comparison include ECHO and MUGA; both procedures are non-invasive techniques. MUGA utilizes radionuclides that bind to red blood cells; the resulting blood pool can be visualized. The images can be used to assess a variety of cardiac functions; however, it is most commonly used to measure left ventricular ejection fraction. [690] ECHO utilizes ultrasound technology, and like MUGA, it is used to assess several different markers of cardiac function and structure. [691] Since both ECHO and MUGA would be obtained separate from an office visit during routine breast cancer surveillance, their use results in a slight disutility to compensate for patient time and convenience. The disutility estimate was obtained from the SF-6D. The instrument contains an item representing "social functioning" which includes a response choice that states "*your health limits your social activities a little of the time*". This response was selected as it was determined to most closely represent the commitment to the additional testing required. The score associated with this item response is -0.055.[692] The listed estimate appeared somewhat high since the disutility is primarily due to the time commitment of the actual test plus transit time, therefore, the base estimate used was 0.025 for each additional appointment required (range 0.020 to 0.030). Both tests are typically used to obtain an estimation of left-ventricular ejection fraction (LVEF), where a normal value is considered to be ≥ 55%. [693] The use of MUGA also involves the use of

[689] M. R. Cowie et al., "Clinical Applications of B-type Natriuretic Peptide (BNP) Testing," *European Heart Journal* 24, no. 19 (2003): 1710.

[690] Danias and Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction."

[691] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

[692] Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes*.

[693] Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure."

[99]Technetium, which often limits repetition due to exposure to additional radiation. [694] Refer to Chapter Three for additional information regarding monitoring strategies.

5.2.1.2 Objective Two

Objective two was to estimate the incidence of cardiac dysfunction in breast cancer patients. The reported incidence of cardiac dysfunction varies significantly. The most frequently cited incidence estimates are dose-dependent, which in older reviews were 3, 7, and 18 percent at doses of 400, 550, and 700 mg/m^2 respectively.[695] Newer evidence suggests that these estimates may be low. More recent dose-dependent values of 5, 26, and 48 percent at doses of 400, 550, and 700 mg/m^2, respectively, have been noted[696]. The entire spectrum of values range from a low of about 1 percent up to 57 percent; the estimate of 57 percent was from a prospective study that followed a cohort of patients for fifteen years, which incidentally is the length of time patients are considered at risk for heart failure development. [697] After it was discovered that anthracyclines have the potential to cause cardiac dysfunction, clinical trials began reporting this adverse effect. However, the follow-up associated with a clinical trial usually ends when the trial ends, the adverse effects from chemotherapy experienced by these patients is often underestimated. There are many contributing factors to the development of cardiac dysfunction including total cumulative dose, prior radiation, and treatment with trastuzumab, all of which can be

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[694] Danias and Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction."

[695] Von Hoff et al., "Risk Factors for Doxorubicin-lnduced Congestive Heart Failure."

[696] Swain, Whaley, and Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin."

[697] Lipshultz and Colan, "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer."

controlled for in a clinical trial but may be experienced by typical patients receiving treatment.[698]

The point estimate for the incidence of cardiac dysfunction was 15.4 percent for patients receiving anthracycline therapy and 27 percent for patients receiving additional trastuzumab[699]. Both are medians for the range of published incidence estimates for each treatment group. The incidence ranges used in this study for the patients receiving anthracyclines and those receiving additional trastuzumab were 10 – 20 percent and 20 – 34 percent, respectively. These ranges were selected to encompass the realistic reported incidence values reported in publications. For patients receiving anthracyclines, a range of 10 – 20 percent should be a realistic representation of incidence estimation when the reported range is 1 to 57 percent. For patients receiving trastuzumab, the majority of reports cite incidence estimates of 27 percent or 34 percent; the lower value of 20 percent was selected to keep the interval equal (i.e., $27\% \pm 7\%$). Refer to Chapter Two for a more detailed discussion on cardiac dysfunction in breast cancer patients. [700]

[698] Swain, Whaley, and Ewer, "Congestive Heart Failure in Patients Treated with Doxorubicin"; Yeh et al., "Cardiovascular Complications of Cancer Therapy."

[699] S. Palmeri et al., "Doxorubicin-Docetaxel Sequential Schedule: Results of Front-Line Treatment in Advanced Breast Cancer," *Oncology* 63, no. 3 (2002): 205–212; Dennis J. Slamon et al., "Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2," *N Engl J Med* 344, no. 11 (September 29, 2001): 783–792.

[700] Slamon et al., "Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2."

5.2.1.3 Objective Three

Objective three was to estimate the costs of using each monitoring strategy. The costs of using each monitoring strategy was estimated using Medicare reimbursement values for the calendar year 2010; these values were obtained via the CMS website (http://www.cms.gov/). The Medicare reimbursement for each natriuretic peptide test is $47.77; therefore, a value of $48 was used. The reimbursement for a complete ECHO (CPT 93306) is $265.07 and the OPPS amount is $533; the mean value of $393 was used. MUGA scanning has several possible CPT codes and Medicare reimbursement amounts range from $261 to $293 with $102.73 add-on. The OPPS amounts range from $357 to $368; $461 was used for estimation (average from reimbursement estimates and OPPS amounts plus $103 add-on amount, cost of irradiated cells (codes for [99]Technetium range from A9500 to A9504) were not considered as this value is typically facility specific).

Annual costs of each strategy were calculated based on the test cost estimate and the frequency of testing. Since frequencies change three times during the fifteen-year surveillance period, they are divided into three intervals. During interval one, patients are tested four times per year, this interval represents years one through three. Interval two represents years four and five and patients are tested twice annually. Interval three represents the remaining years (six through fifteen) where patients are tested once annually. Table 5.1 below lists each monitoring alternative, the cost of a single test and the annual cost of each strategy during each interval of surveillance. Refer to Chapter Four for more detailed information regarding associated costs.

Table 5.1 Annual Cost of Each Monitoring Strategy for the Development of Cardiac Dysfunction During Each Interval of Surveillance

		Single Test[1]	Interval 1	Interval 2	Interval 3
Strategy	*BNP*	48	192	96	48
	ECHO	393	1,572	786	393
	MUGA	461	1,844	922	461

[1] Single Test Cost Was Obtained from Estimates of Medicare Reimbursement; http://www.cms.gov/; Refer to Chapter Four for Additional Information. Interval 1 is surveillance years 1-3 where patients are seen quarterly. Interval 2 corresponds to years 4 and 5 where patients are seen twice annually. Interval 3 corresponds to years 6 -15 where patients are seen annually

5.2.2   OBJECTIVES WITH TESTABLE HYPOTHESES

5.2.2.1 Objective Four

Objective four was to estimate the direct costs of treating cardiac dysfunction discovered as a result of monitoring with each alternative. The hypothesis tested for this objective is that the average direct costs of treating cardiac dysfunction as a result of BNP will be greater than the strategy of doing nothing, but less than using either ECHO or MUGA.

- No Monitoring $_{\text{direct cost}}$ < BNP $_{\text{direct cost}}$

- BNP $_{\text{direct cost}}$ < ECHO $_{\text{direct cost}}$

- BNP $_{\text{direct cost}}$ < MUGA $_{\text{direct cost}}$

The direct costs of treating cardiac dysfunction included the cost of medications, medication management, outpatient office visits, potential hospitalizations and emergency department visits. Costs of treatment are highly dependent on whether the patient is experiencing symptoms. The average direct costs resulting from monitoring with BNP is $10,062 which when compared with doing nothing, has an incremental cost of -$3,565. This indicates that monitoring with BNP costs less than No Monitoring, leading to the rejection of the first hypothesis for this objective. The average direct costs of treatment resulting from the use of ECHO and MUGA are $14,639 and $15,656, respectively. The ladder two hypotheses are accepted as the averages costs for both ECHO and MUGA are greater than the average cost of BNP. Table 5.2 lists the average direct cost resulting from each strategy.

Table 5.2 Average Direct Costs and Incremental Costs from Base-Case Analysis

Strategy	Average Direct Cost ($)	Incremental Cost ($)
BNP	10,062	
No Monitoring	13,627	3,565
ECHO	14,639	4,677
MUGA	15,656	5,593

Costs in 2010 U.S. Dollars

5.2.2.2 Objective Five

Objective five was to estimate the difference in QALY's gained between monitoring strategies. The hypothesis for this objective is that the QALY associated with the use of natriuretic peptides is greater than the options being compared (i.e., doing nothing, ECHO and MUGA).

- No Monitoring $_{QALY}$ < BNP $_{QALY}$
- ECHO $_{QALY}$ < BNP $_{QALY}$
- MUGA $_{QALY}$ < BNP $_{QALY}$

In the base-case analysis, BNP had an average effectiveness of 6.92 which is a gain of 2.70 QALY's when compared to the alternative of doing nothing. The average effectiveness of ECHO and MUGA were 6.61 and 6.49 QALY's respectively. The comparison of BNP to ECHO and MUGA results in gains of 0.31 and 0.43 QALY's respectively. All three hypotheses are accepted, the average QALY gained from BNP was greater than all three alternative strategies. The average effectiveness of each strategy is listed in the results of the base-case analysis in Table 5.3.

Table 5.3: Average and Incremental Effectiveness from Base-Case Analysis

Strategy	Effectiveness (QALY)	I.E. (QALY)
BNP	6.92	
No Monitoring	4.22	-2.70
ECHO	6.61	-0.31
MUGA	6.49	-0.43

I.E: Incremental Effectiveness; QALY: Quality-Adjusted Life-Year

5.2.2.3 Objective Six

Objective six was to determine the incremental cost-effectiveness (ICER) of using BNP versus other comparators as measured by the percent of patients diagnosed. The hypothesis for this objective is that when effectiveness is measured by the percentage of patients diagnosed, the ICER of using BNP versus the alternative strategies would show that BNP is the dominant strategy.

- ECHO $_{\% \text{ Diag}}$ < BNP $_{\% \text{ Diag}}$, BNP $_{\text{cost}}$ < ECHO $_{\text{cost}}$
- MUGA $_{\% \text{ Diag}}$ < BNP $_{\% \text{ Diag}}$, BNP $_{\text{cost}}$ < MUGA $_{\text{cost}}$
- Both of the above scenarios would result in negative ICER values

To determine the percentage of patients diagnosed for each testing modality, one must consider that the model structure allows patients to be diagnosed in asymptomatic or symptomatic stages, however, patients can also transition from the asymptomatic stage to the symptomatic stage as a function of disease progression. Therefore because patients residing in the symptomatic stage have multiple sources, only patients "Diagnosed ASX" was considered to determine the percentage of patients diagnosed for purposes on analysis. The percent of patients diagnosed is expressed by using the maximum percentage of patients residing in the "Diagnosed ASX" state as determined by Markov Cohort Analysis. Since each test has separate branches for HER-2 (+) and (-) patients, each had to be analyzed as separate cohorts. The cumulative cost from each cohort analysis was used as the cost to determine ICER for each alternative. Tables 5.4 and 5.5 below list the results from the Markov Cohort Analyses. The diagnosed percentages for BNP were 21.8 and 31.6 for HER-2 (-) and HER-2 (+), respectively. The percentages for ECHO and MUGA were lower in both HER-2 (+) and (-) patients and corresponding costs were higher. The resulting ICER values indicate that BNP is the absolute dominant alternative when compared to either ECHO or MUGA; therefore, both hypotheses for this objective are accepted.

Table 5.4 Maximum Probability HER-2 (-) Patients Residing in Diagnosed Asymptomatic Stage with Associated Cumulative Costs

Strategy	ASX (%)	I.E	Cost ($)	I.C.	ICER
BNP	21.8		9,785		
ECHO	20.8	-1.0	14,696	4,911	-4,911
MUGA	21.7	-0.1	15,702	5917	-59,170

ASX (%) is the maximum percentage of patients residing in the "Diagnosed ASX" state; Cost is the cumulative cost for each Markov Cohort Analysis at Stage 15; I.E.: Incremental Effectiveness; I.C.: Incremental Cost; ICER: Incremental Cost-Effectiveness Ratio

Table 5.5 Maximum Probability HER-2 (+) Patients Residing in Diagnosed Asymptomatic Stage with Associated Cumulative Costs

Strategy	ASX (%)	I.E	Cost ($)	I.C.	ICER
BNP	31.6	-	10,893	-	-
ECHO	29.7	-1.9	14,870	3,977	-2,093
MUGA	31.5	-0.1	15,517	4,624	-46,240

ASX (%) is the maximum percentage of patients residing in the "Diagnosed ASX" state; Cost is the cumulative cost for each Markov Cohort Analysis at Stage 15, I.E.: Incremental Effectiveness, I.C.: Incremental Cost, ICER: Incremental Cost-Effectiveness Ratio

5.2.2.4 Objective Seven

Objective seven was to determine the incremental cost-utility of using BNP versus other comparators as measured by QALYs. The hypothesis for this objective is when comparing BNP to the alternatives, the incremental cost-utility results in an ICER that is below the WTP threshold of $50,000.

- BNP vs. No Monitoring; ICER < $50,000 WTP per QALY
- BNP vs. ECHO; ICER < $50,000 WTP per QALY
- BNP vs. MUGA; ICER < $50,000 WTP per QALY

The results of the base-case cost-effectiveness analysis are listed in Table 5.6 and are illustrated in Figure 5.1. The base-case was calculated using a discount rate of 3 percent for costs and outcomes. The effectiveness of each strategy is measured in QALY's and costs are in 2010 U.S. dollars. BNP yielded an average effectiveness of 6.92 QALY's, which is greater than the average effectiveness of all competing strategies with 4.22, 6.61 and 6.49 QALY's for No monitoring, ECHO, and MUGA, respectively. The average cost of monitoring with BNP is $10,062 compared to $13,627, $14,739 and $15,656 for No Monitoring, ECHO, and MUGA, respectively. The resulting ICER values are therefore negative for all alternatives compared to BNP, leading to the acceptance of all three tested hypotheses.

Table 5.6 Base-Case Cost-Effectiveness of Strategies Compared to BNP

Strategy	Cost ($)	I.C. ($)	Eff.	I.E.	ICER	C/E
BNP	10,062		6.92			1,454
Nothing	13,627	3,565	4.22	-2.70	-1,322	3,226
ECHO	14,739	4,677	6.61	-0.31	-14,888	2,231
MUGA	15,656	5,593	6.49	-0.43	-12,964	2,413

Cost in U.S. dollars, Effectiveness in QALY's; Eff.: Effectiveness; I.C. = Incremental Cost,
I.E. = Incremental Effectiveness, ICER = Incremental Cost-Effectiveness Ratio,
C/E = Cost-Effectiveness

Figure 5.1 Base-Case Cost-Effectiveness Analysis of Monitoring Strategies

Cost-Effectiveness Analysis
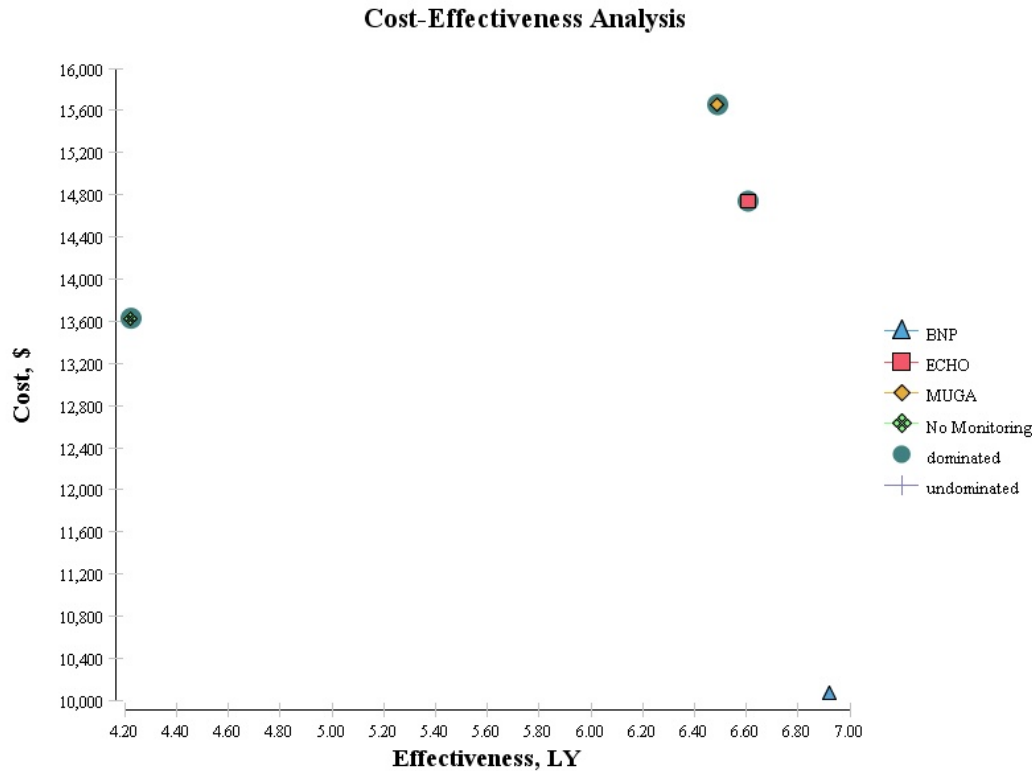
5.3 Sensitivity Analyses:

Several sensitivity analyses were performed to determine the robustness of results. One-way sensitivity analyses included analyzing varying discount rates (0-5%), varying the probability of testing HER-2 positive (20-30%), varying the incidence of cardiac dysfunction in both anthracycline-only regimens (10-20%) and trastuzumab regimens (20 – 34%), and disutilities for additional tests (0.020 – 0.030) The summary of the results from one-way sensitivity analyses are listed in Tables 5.7 - 5.11. Results from each of those analyses are listed in their entirety in Appendix F. Tornado Diagrams were constructed to examine the effect of varying all values for transition probabilities, mortality, utility, costs and test characteristics. Resulting tornado diagrams are listed in Figures 5.2 – 5.8. The ranges used are listed in Appendix E, Tables E.1 - E.4. A probabilistic sensitivity analysis was conducted utilizing a Monte Carlo Simulation with 10,000 iterations. Distributions were created for all study variables; gamma distributions were used for costs and beta distributions were used for probabilities and utilities.

5.3.1 ONE-WAY SENSITIVITY ANALYSES:

One-way sensitivity analyses were conducted with variables ranges for discount rate, the disutility estimate, the probability of testing HER-2 positive, incidence of cardiac dysfunction with anthracycline-based therapy, incidence of dysfunction with the addition of trastuzumab to anthracycline-based regimens, and the probability of a patient being diagnosed in an asymptomatic stage. Table 5.7 below lists the results from the analysis of variable discount rate. The base-case analysis was performed with a discount rate of 3 percent and was varied from 0 to 5 percent. Each alternative strategy when

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compared to BNP had a negative ICER value, indicating that BNP is the absolute

dominant strategy.

Table 5.7 Summary of CE and ICER for 0, 3, and 5% Discount Rates

		C/E ($)			ICER($/QALY)		
	DR	0%	3%	5%	0%	3%	5%
Strategy	*BNP*	1,369	1,454	1,512	-	-	-
	No	3,115	3,226	3,300	-1,024	-1,322	-1,539
	ECHO	2,087	2,231	2,327	-15,344	-14,888	-14,661
	MUGA	2,255	2,413	2,517	-12,598	-12,964	-13,195

DR: Discount Rate, C/E: Cost-Effectiveness Ratio, ICER: Incremental Cost-Effectiveness Ratio

Table 5.8 below illustrates the summary of results of the one-way sensitivity analysis of varying the probability of testing positive for HER-2. The base-case analysis used a probability of 25 percent; sensitivity analysis examined a range of 20 – 30 percent. Similar to the results of the analysis with varying discount rate, the cost-effectiveness ratio for BNP remains the absolute dominant strategy the range of values for HER-2 positive probability.

Table 5.8 Summary of CE and ICER for HER-2 (+) Rates of 20, 25 and 30%

	HER-2%	CE ($)			ICER ($/QALY)		
		20%	25%	30%	20%	25%	30%
Strategy	*BNP*	1,432	1,454	1,476			
	No	3,226	3,226	3,226	-1,310	-1,322	-1,335
	ECHO	2,203	2,231	2,254	-14,853	-14,888	-14,924
	MUGA	2,390	2,413	2,435	-13,042	-12,964	-12,884

HER-2%: Percentage of Patients Testing Positive for HER-2 Overexpression,
C/E: Cost-Effectiveness, ICER: Incremental Cost-Effectiveness

Table 5.9 below lists the results of one-way sensitivity analysis examining the range of potential incidence values for cardiac dysfunction with anthracycline-only regimens, as well as varying incidence values with the addition of trastuzumab. The base-case used an incidence value of 0.154 for anthracycline-only therapy with a range of 0.10 to 0.20. The incidence of cardiac dysfunction with the addition of trastuzumab was estimated at 0.25 in the base-case analysis, with a range from 0.20 to 0.34. Results are consistent with the previous one-way sensitivity analyses, since ICER results for all alternative strategies are negative; BNP is the absolute dominant strategy.

Table 5.9 Summary of CE and ICER for Varying Incidence Values

		CE ($)			ICER ($/QALY)		
	Incidence_AC	**0.10**	**0.154**	**0.20**	**0.10**	**0.154**	**0.20**
	BNP	1,180	1,454	1,636			
	No	3,226	3,226	3,226	-1,320	-1,322	-1,397
	ECHO	1,943	2,231	2,420	-14,421	-14,888	-15,199
	MUGA	2,120	2,413	2,604	-13,686	-12,964	-12,413
Strategy	**Incidence_T**	**0.20**	**0.27**	**0.34**	**0.20**	**0.27**	**0.34**
	BNP	1,401	1,454	1,488			
	No	3,226	3,226	3,226	-1,282	-1,322	-1,366
	ECHO	2,177	2,231	2,264	-14,810	-14,888	-14,928
	MUGA	2,359	2,413	2,444	-13,181	-12,964	-12,783

C/E: Cost-Effectiveness, ICER: Incremental Cost-Effectiveness Ratio, Incidence_AC: incidence of cardiac dysfunction with anthracycline-based treatment; Incidence_T: incidence of cardiac dysfunction when trastuzumab is added to anthracyclines

Table 5.10 below summarizes the results from the one-way sensitivity analysis with varying estimates that patients will be diagnosed in an asymptomatic stage. The base-case analysis used an estimate of 0.7505, and the sensitivity analysis used a range of 0.716 to 0.785. Similar to the previous one-way sensitivity analyses, the resulting ICER values for all other alternatives are negative; therefore, BNP is the absolute dominant strategy over the range of probability estimates.

Table 5.10 Resulting CE and ICER Values for Varying Estimates That Patients will be Diagnosed Asymptomatic

		CE ($)			ICER ($/QALY)		
	P_Diag_ASX	0.716	0.795	0.875	0.716	0.795	0.875
Strategy	*BNP*	1,471	1,454	1,437			
	No	3,226	3,226	3,226	-1,360	-1,322	-1,284
	ECHO	2,257	2,231	2,206	-15,174	-14,888	-14,294
	MUGA	2,442	2,413	2,384	-13,035	-12,964	-12,973

C/E: Cost-Effectiveness; ICER: Incremental Cost-Effectiveness; p_diag_asx: probability that a patient will be diagnosed in an asymptomatic stage

Table 5.11 below shows the results of a one-way sensitivity analysis of varying the disutility estimate accounting for additional time required by the patients. The base-case estimate for utility was 0.025 and the range used for sensitivity analysis was 0.02 to 0.03. The results are similar to all previous sensitivity analyses, leaving BNP as the only viable alternative as all other strategies have negative ICER values.

Table 5.11 Resulting CE and ICER Values for Each Alternative for Varying Disutility Estimates

		CE ($)			ICER ($/QALY)		
	Disutility	**0.02**	**0.025**	**0.03**	**0.02**	**0.025**	**0.03**
Strategy	*BNP*	1,454	1,454	1,454	-	-	-
	No	3,226	3,226	3,226	-1,322	-1,322	-1,322
	ECHO	2,201	2,231	2,262	-20,901	-14,888	-11,562
	MUGA	2,380	2,413	2,446	-16,334	-12,964	-10,746

C/E: Cost-Effectiveness, ICER: Incremental Cost-Effectiveness

Tornado Diagrams were constructed to analyze any differences in results by varying estimates for categories of variables. Categories that were examined include transition probabilities, mortality, utilities, costs, and test characteristics. The resulting tornado diagrams are illustrated in Figures 5.2 to 5.6. Ranges used for each variable are listed in Appendix F, Tables F.1 - F.4. Figure 5.2 below shows the results of varying the probabilities of state transitions. The diagram shows that varying the probabilities of hospitalization and readmission had the greatest effect on the net benefit. With both of these variables, the outcomes remained insensitive to the variation in probabilities. BNP was the absolute dominant strategy over all other alternatives regardless of the probability of hospitalization or readmission.

Figure 5.2 Tornado Diagram Illustrating Effects of Varying Transition Probabilities

Tornado Analysis (Net Benefits)

p_Hosp (0.188 to 0.23)
p_Readmit (0.196 to 0.37)
p_ASXtoSX_TX (0.05 to 0.1)
p_ED (0.038 to 0.046)
p_ASXtoSX_noTX (0.05 to 0.15)

EV: 335951.85950582335

332000 333000 334000 335000 336000 337000 338000 339000 340000 341000
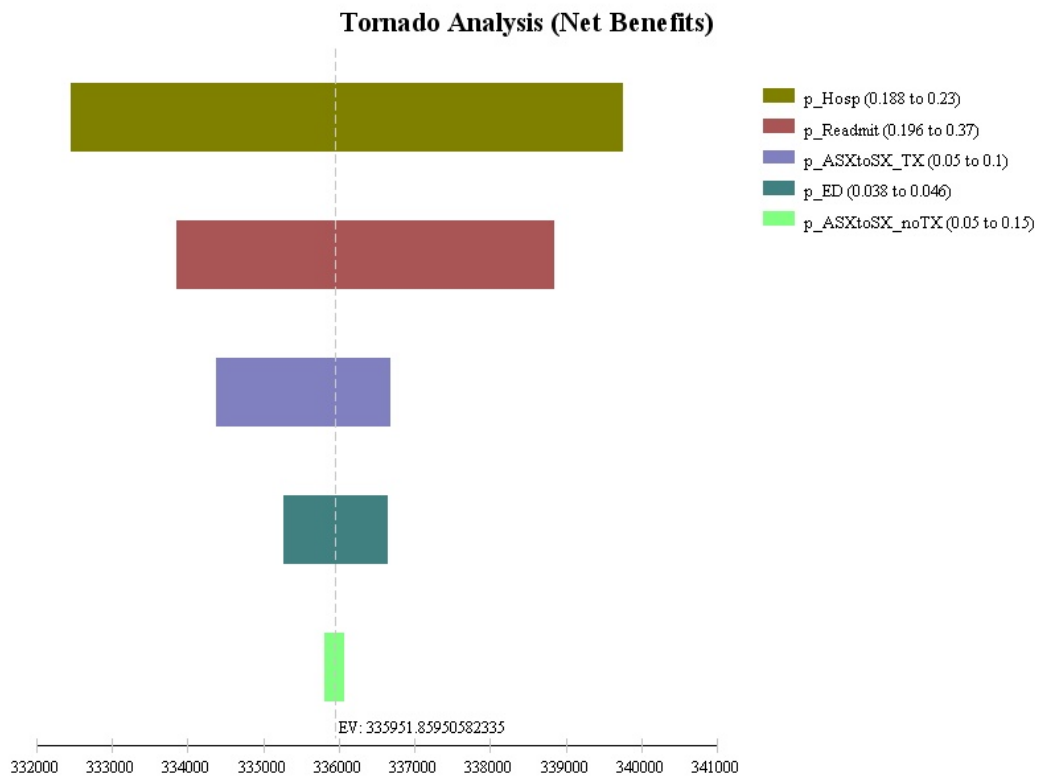
Figure 5.3 below illustrates the results when varying the estimates for all mortality variables. The results indicate that varying the estimates for mortality in Stages D and A have the greatest effect on cost-effectiveness. Similar to the results for transition probabilities, though mortality estimates in Stages D and A showed the greatest variation in net benefits, BNP remained the absolute dominant strategy over all other alternatives over the range of estimates.

Figure 5.3 Tornado Diagram with Varying Estimates for Mortality:

Tornado Analysis (Net Benefits)

Legend:
- p_Death_D (0.113 to 0.316)
- p_Death_A (0.0020 to 0.012)
- p_Death_postDC (0.162 to 0.312)
- p_Death_B (0.0050 to 0.012)
- p_Death_C (0.043 to 0.072)
- p_Death_Hosp (0.056 to 0.068)

EV: 335951.85950582335

328000 330000 332000 334000 336000 338000 340000 342000 344000 346000 348000 350000 352000
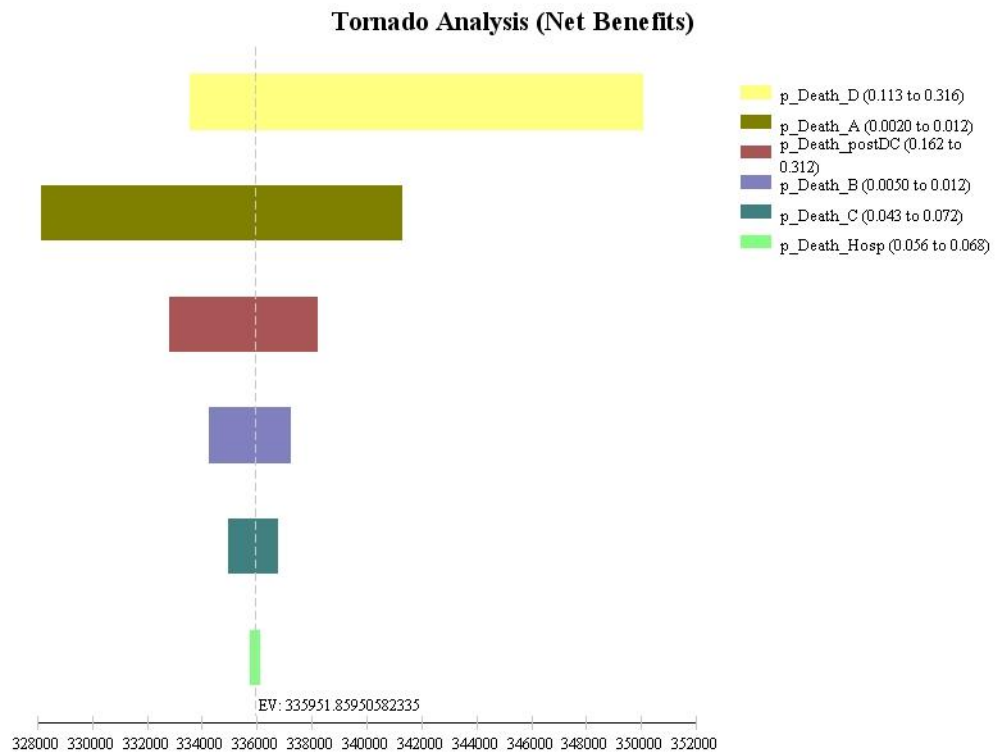
Figure 5.4 below illustrates the results when varying estimates for all utility variables. The tornado diagram shows that the estimates for the utility during hospitalization have the greatest effect on cost-effectiveness. The cost-effectiveness through the range of estimates for utility during hospitalization is highly variable; however, when comparing the different alternatives, BNP remains an absolute dominant strategy over all other.

Figure 5.4 Tornado Diagram for Varying Utility Estimates

Tornado Analysis (Net Benefits)

Legend:
- u_Hosp (0.48 to 0.8)
- u_BNP_CD (0.624 to 0.795)
- u_BNP_B (0.852 to 0.877)
- u_disutil (0.02 to 0.03)

EV: 335951.85950582335

332000 334000 336000 338000 340000 342000 344000 346000 348000 350000
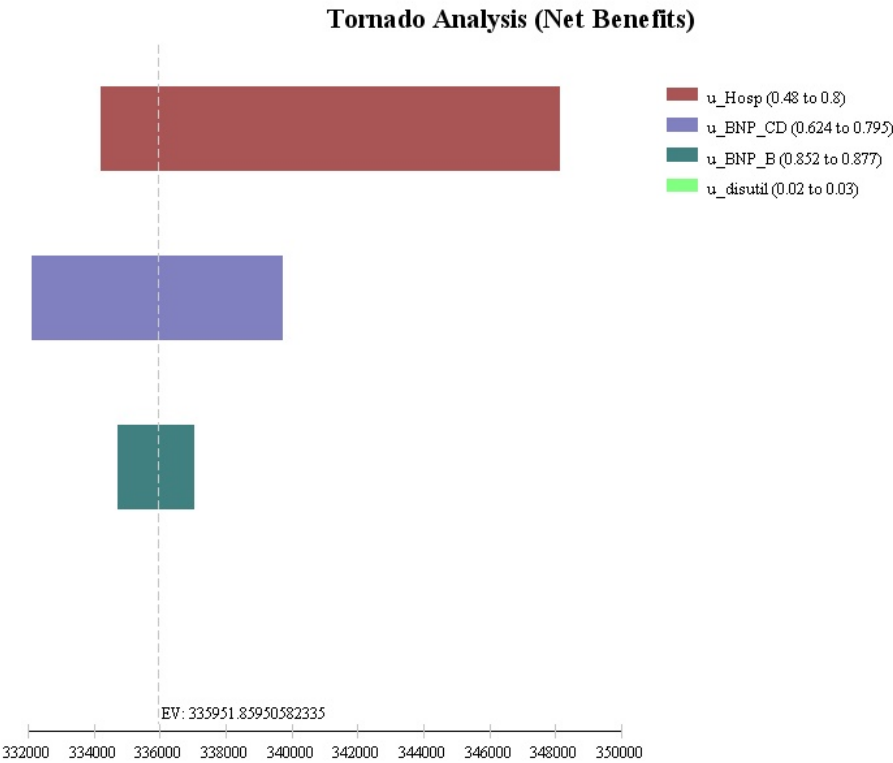
Figure 5.5 illustrates the results when varying the estimates for all cost variables. The estimates for the cost of hospitalization had the greatest effect on cost-effectiveness, likely because it has the largest range of estimates. Consistent with other prior tornado analyses, these results were insensitive to the variation in cost estimates.

Figure 5.5 Tornado Diagram Representing Varying Estimates for Cost Variables

Tornado Analysis (Net Benefits)

c_hosp (4200.0 to 9600.0)
c_office_est (27.0 to 117.0)
c_meds_ASX (206.0 to 407.0)
c_BNP (40.0 to 58.0)
c_meds_SX (1039.0 to 1285.0)
c_MM (57.0 to 69.0)
c_ED (70.0 to 190.0)
c_office_new (81.0 to 137.0)
c_MUGA (372.0 to 500.0)
c_ECHO (265.0 to 522.0)

EV: 335951.85950582335

333000 333500 334000 334500 335000 335500 336000 336500 337000 337500 338000 338500
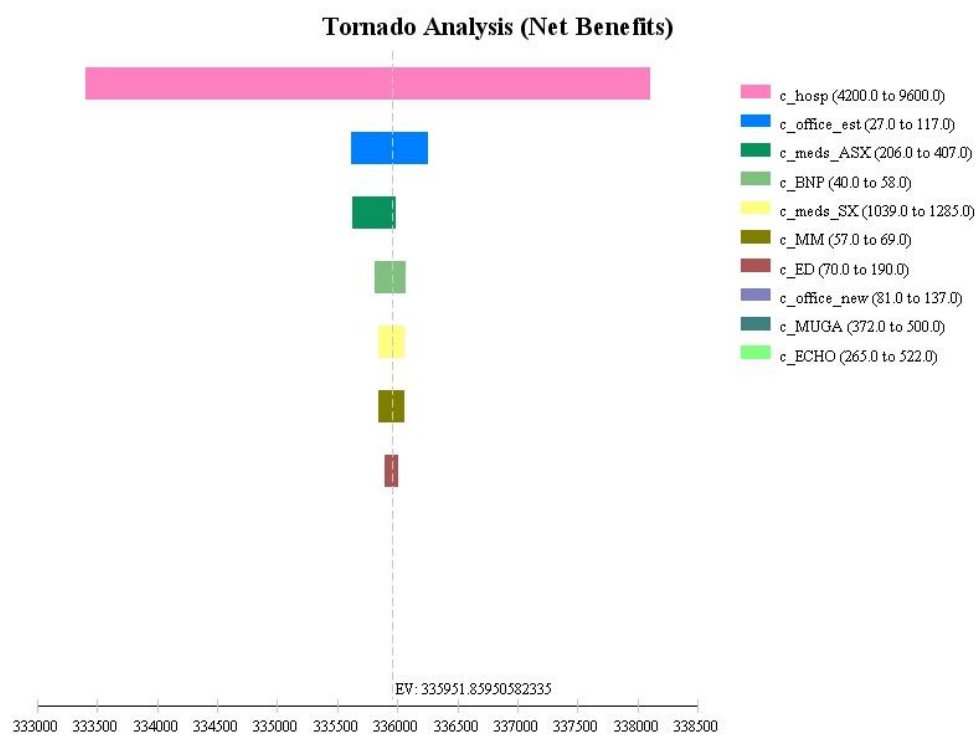
Figure 5.6 illustrates the results when estimates for test characteristics are varied for the three tests being compared. Characteristics of ECHO and MUGA did not have any effect on the results of the cost-effectiveness analysis, while the sensitivity of BNP had the greatest effect, although BNP remained the absolute dominant strategy over all other alternatives through the range of estimates.

Figure 5.6 Tornado Diagram Representing Varying Estimates for Test Characteristics

Tornado Analysis (Net Benefits)

BNP_Sensitivity (0.91 to 0.95)
BNP_Specificity (0.63 to 0.83)
MUGA_Specificity (0.65 to 0.79)
MUGA_Sensitivity (0.88 to 0.92)
ECHO_Specificity (0.75 to 0.87)
ECHO_Sensitivity (0.62 to 0.66)

EV: 335951.85950582335

335400 335500 335600 335700 335800 335900 336000 336100 336200 336300 336400 336500
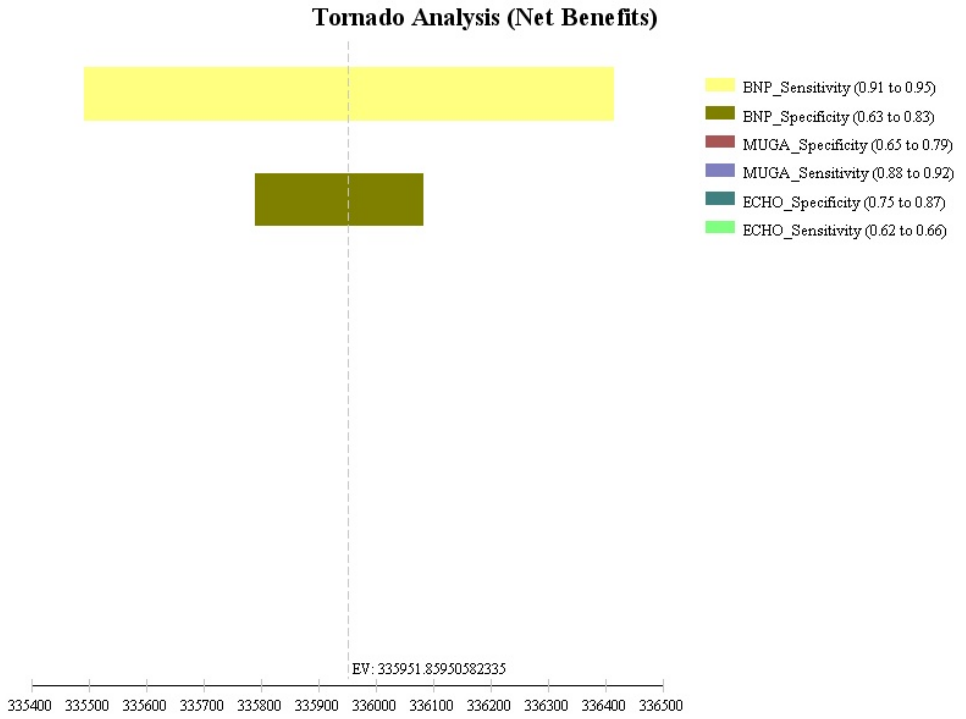
5.3.2   SUMMARY OF ONE-WAY SENSITIVITY ANALYSES:

One-way sensitivity analyses were performed for varying discount rate, probability of testing HER-2 positive, and incidence of cardiac dysfunction with anthracycline-based regimens ± trastuzumab, the probability a patient will be diagnosed in an asymptomatic stage and the disutility estimate for additional testing. Additionally, tornado diagrams were constructed for the variation in estimates by category (i.e. costs, utilities, etc.). Results from each of these analyses were consistent, regardless of the variable; BNP remained the absolute dominant strategy over all other alternatives.

5.3.3   PROBABILISTIC SENSITIVITY ANALYSIS:

A probabilistic sensitivity analysis was conducted utilizing a Monte Carlo Simulation where utilities and probabilities were varied using beta distributions; costs were varied using gamma distributions for 10,000 iterations. The ranges of estimates for each variable were the same as those used for one-way sensitivity analyses. Table 5.9 summarizes the results from the probabilistic sensitivity analysis. Figure 5.7 graphs the

overall mean cost-effectiveness and Figure 5.8 shows the cost-effectiveness scatterplots resulting from the probabilistic sensitivity analysis when comparing all strategies. The mean costs for each alternative are \$6,441 (SD \$9,898, Range 0.15 – 163,690), \$12,209 (SD 17,589, Range 0 – 190,105), \$13,159 (SD 20,270, Range 0 – 367,070) and \$14,208 (SD 20,563, Range 10.33 – 289,478) for BNP, ECHO, MUGA and No Monitoring respectively. The mean effectiveness values are 8.72 (SD 2.50, Range 3.28 – 11.73), 8.31 (SD 2.52, Range - 3.08 – 11.73), 8.24 (SD 2.58, Range -2.99 – 11.73) and 4.26 (SD 0.35, Range 2.90 – 5.69) for BNP, ECHO, MUGA and No Monitoring respectively. BNP had the lowest average cost and the highest average effectiveness. When comparing BNP to the other strategies, the ICER's were -\$14,179/QALY, -\$14,053/QALY and -\$1,744/QALY for ECHO, MUGA and No Monitoring respectively.

Table 5.9 Summary of Results from Monte Carlo Simulation

Alternative	COST	EFF	IC	IE	ICER
BNP	\$6,441	8.719	-	-	-
ECHO	\$12,209	8.312	\$5,768	-0.407	-\$14,179
MUGA	\$13,159	8.241	\$6,718	-0.478	-\$14,053
No Monitoring	\$14,208	4.265	\$7,768	-4.454	-\$1,744

Eff: Effectiveness; IC: Incremental Cost; IE: Incremental Effect;
ICER: Incremental Cost-Effectiveness Ratio

Figure 5.7   Mean Cost-Effectiveness of All Monitoring Strategies

Cost-Effectiveness Analysis
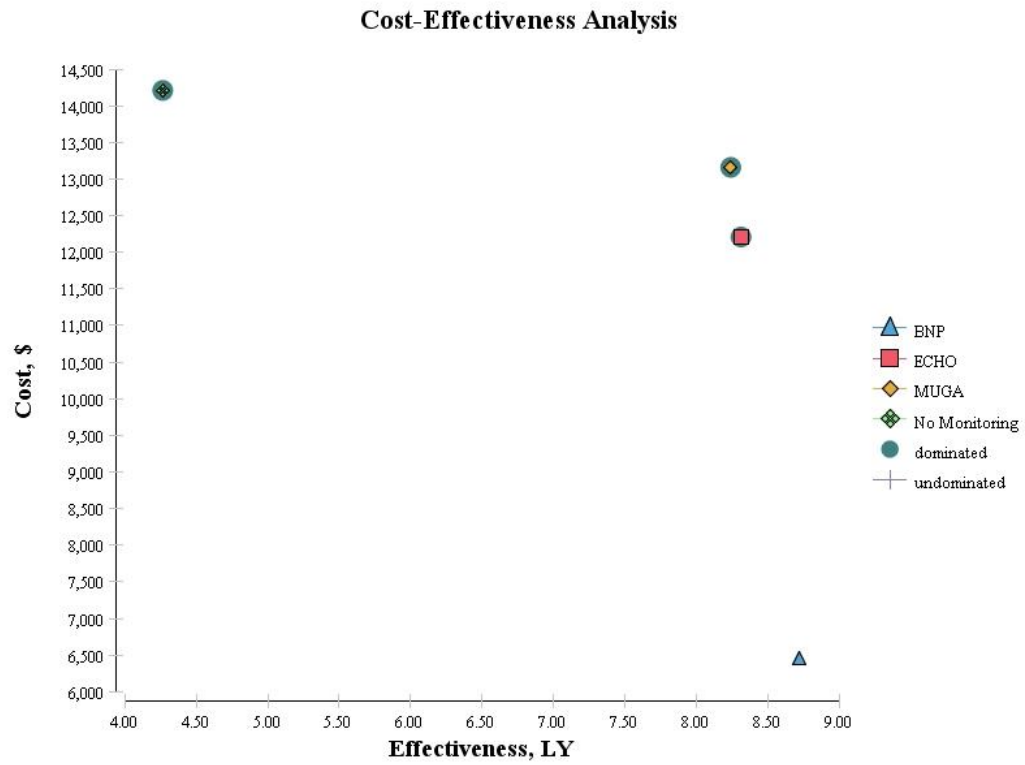
Figure 5.8 Cost-Effectiveness Scatterplot of All Monitoring Strategies

CE Scatterplot of All Monitoring Strategies
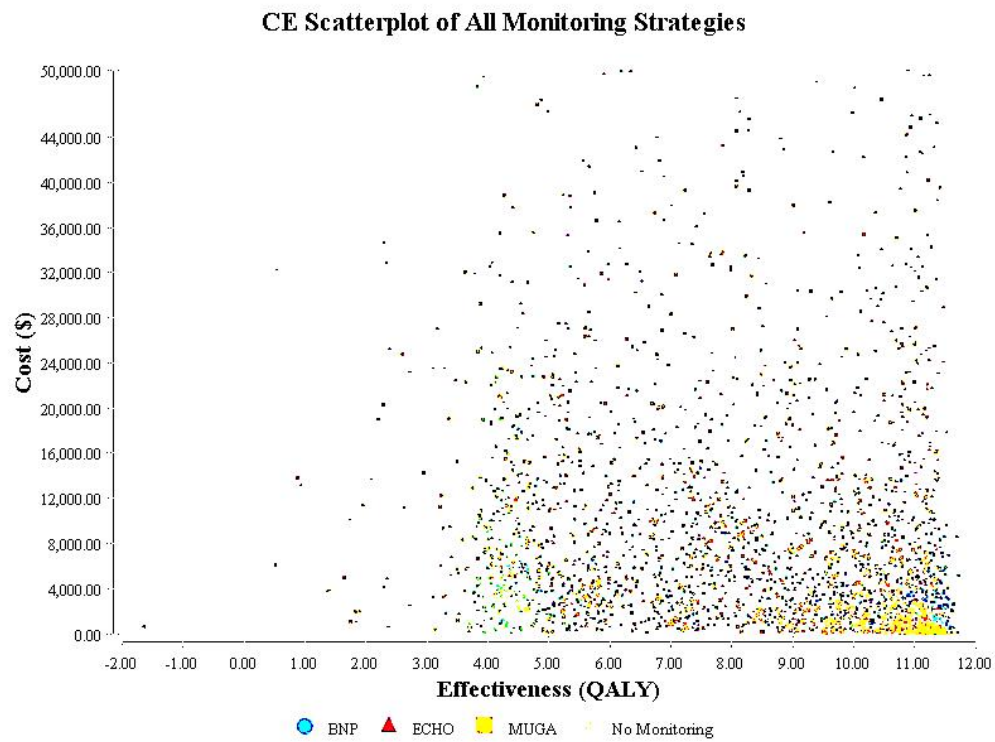
Figures 5.9, 5.10 and 5.11 illustrate the incremental cost-effectiveness scatterplots for the comparisons of BNP with each other monitoring strategy. Each scatterplot lists the percentage of iterations that fall in quadrant IV which represents the proportion that BNP is an absolute dominant strategy.   Those proportions are 32%, 45% and 74% for ECHO, MUGA and No Monitoring respectively. With the addition of areas where BNP leads to an ICER that is below the WTP threshold of $50,000, the proportions where BNP is cost-effective increase to 65.4%, 72.1% and 97.1% for ECHO, MUGA and No Monitoring respectively.

Figure 5.9 Incremental CE Scatterplot – BNP vs. ECHO
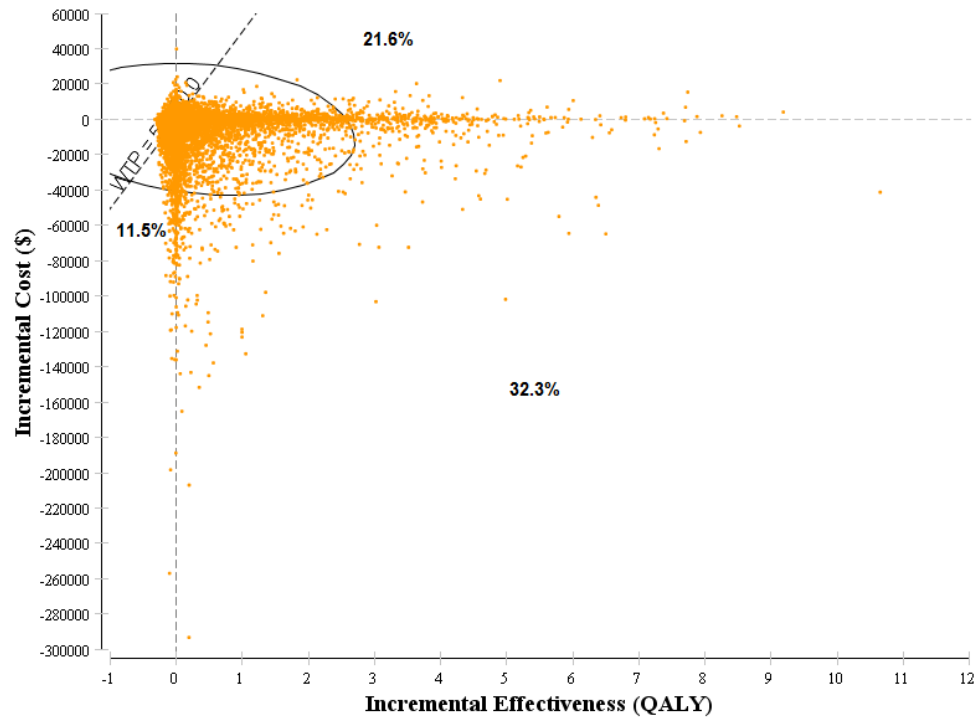
Figure 5.10 Incremental CE Scatterplot – BNP vs. MUGA
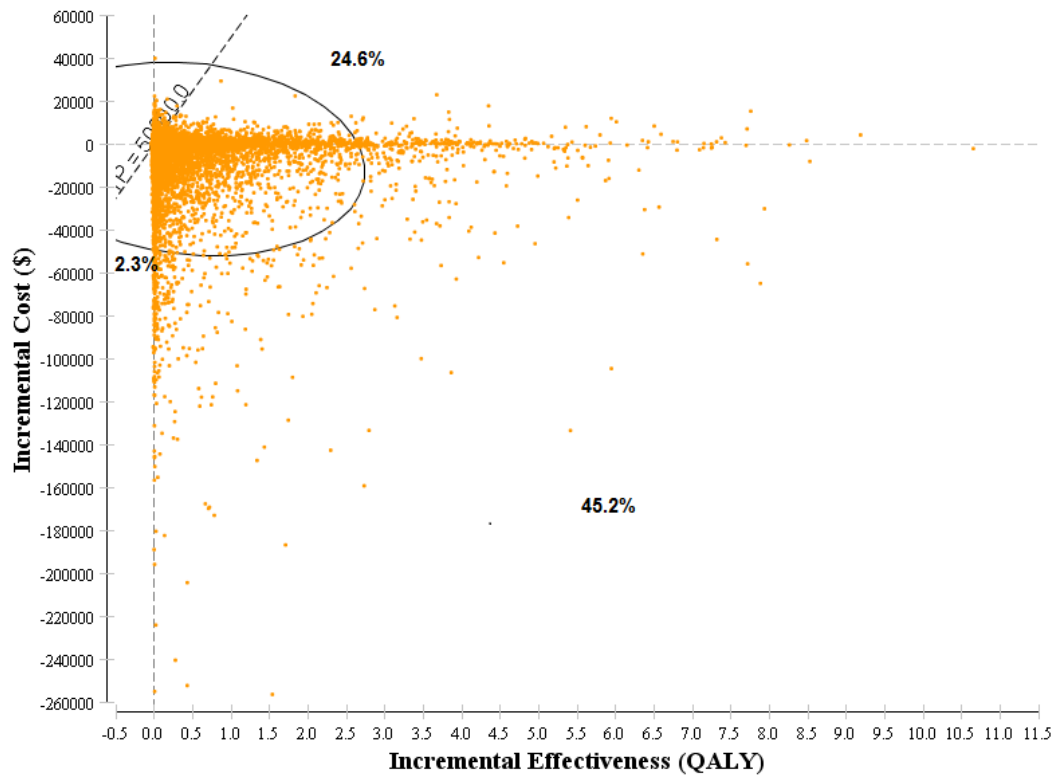
Figure 5.11 Incremental CE Scatterplot BNP vs. No Monitoring
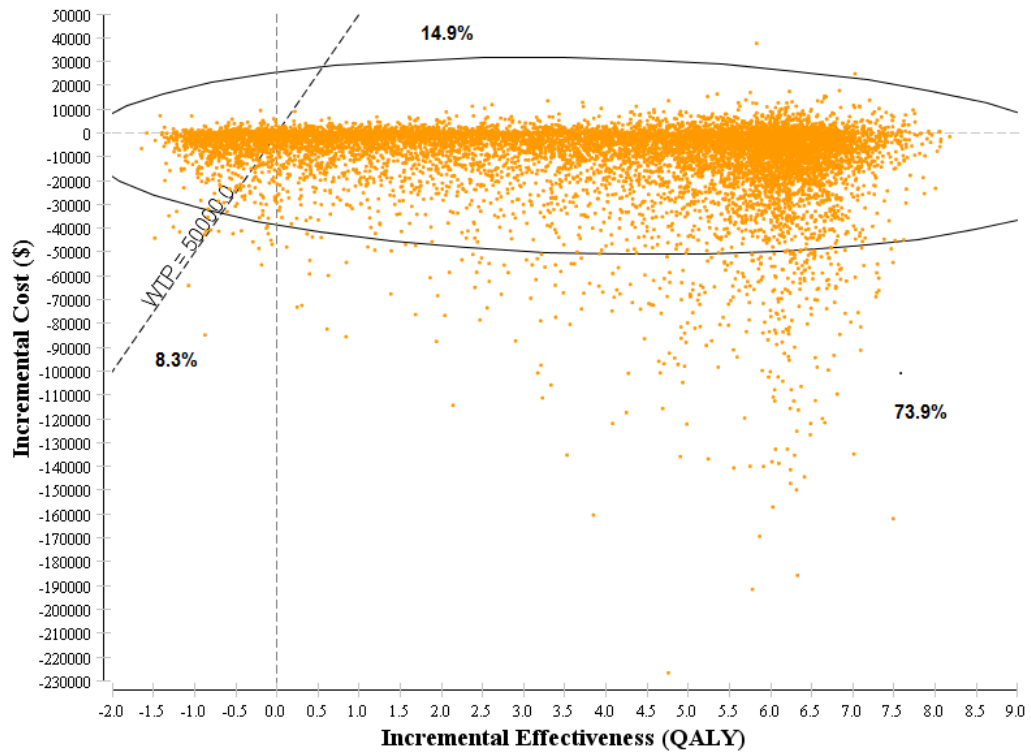
Table 5.10 Summary of Tested Hypotheses

Objective #	Hypothesis	Result
4	No Monitoring $_{\text{direct cost}}$ < BNP $_{\text{direct cost}}$	Rejected
	BNP $_{\text{direct cost}}$ < ECHO $_{\text{direct cost}}$	Accepted
	BNP $_{\text{direct cost}}$ < MUGA $_{\text{direct cost}}$	Accepted
5	No Monitoring $_{\text{QALY}}$ < BNP $_{\text{QALY}}$	Accepted
	ECHO $_{\text{QALY}}$ < BNP $_{\text{QALY}}$	Accepted
	MUGA $_{\text{QALY}}$ < BNP $_{\text{QALY}}$	Accepted
6	ECHO $_{\text{\% Diag}}$ < BNP $_{\text{\% Diag}}$	Accepted
	MUGA $_{\text{\% Diag}}$ < BNP $_{\text{\% Diag}}$	Accepted
7	BNP vs. No Monitoring; ICER < \$50,000 WTP per QALY	Accepted
	BNP vs. ECHO; ICER < \$50,000 WTP per QALY	Accepted
	BNP vs. MUGA; ICER < \$50,000 WTP per QALY	Accepted

CHAPTER SIX: DISCUSSION

6.1   Introduction

This chapter includes a discussion of the base-case results, results of the sensitivity analyses, study limitations, study conclusions and possible directions for future research. This chapter also includes a description of the study population, strategies under comparison and incidence of cardiac dysfunction.

6.2   Population Studied

Breast cancer is the most commonly diagnosed cancer in women in the United States. It is estimated that one in eight women will be diagnosed with breast cancer at some time in their life. Current SEER data is only available through 2008; therefore the number of projected cases for 2010 was used in this study. SEER estimates that there will be a total of 209,060 new cases diagnosed in 2010, including 54,010 *in situ* cases, leaving 155,050 invasive cases. Of those, 1,970 are expected to be men. [701] The population under study is women diagnosed with invasive breast cancer, therefore the hypothetical cohort consists of 153,080 total patients. It is estimated that 25 percent will test positive for HER-2 overexpression; therefore, receiving treatment with trastuzumab in addition to an anthracycline-based chemotherapy regimen. [702] Each treatment arm consists of 114,810 and 38,270 patients in the anthracycline and trastuzumab groups, respectively. The cohort of patients is assumed to have been treated successfully with a result of complete remission. According to the ACC/AHA classification system, patients who have received

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[701] "SEER Web Site", n.d., http://seer.cancer.gov/.

[702] Abeloff et al., "Cancer of the Breast."

cardiotoxic therapy are classified as Stage A.[703] Stage A identifies patients who are at risk of developing heart failure but are currently without symptoms or other evidence of cardiac dysfunction; therefore, all patients in this cohort enter the model in Stage A.

6.3 Strategies Under Comparison

There are three monitoring methods under comparison along with the option of doing nothing. The three monitoring strategies include BNP, ECHO and MUGA. BNP is a hormone produced by the ventricles that primarily assists in fluid regulation. BNP is secreted from the ventricles in response to stretch of myocytes. Increases in BNP levels are proportional to increases in both fluid volume and ventricular dysfunction. BNP levels have also been shown to be elevated in asymptomatic cardiac dysfunction. [704] BNP levels can be obtained from a blood sample, and can be measured via a lab test or a bedside assay. In the study population, this test would be particularly useful as blood samples are already drawn during their routine scheduled follow-up, thus this test can be added to existing labs orders. This level of convenience adds to the appeal of using this strategy to monitor cardiac function. In addition to convenience, results are easily interpreted which demonstrates value to non-cardiologists. [705]

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[703] Hunt et al., "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation."

[704] Aviles and Aviles, "Advances in Cardiac Biomarkers"; de Lemos, McGuire, and Drazner, "B-type Natriuretic Peptide in Cardiovascular Disease."

[705] Cowie et al., "Clinical Applications of B-type Natriuretic Peptide (BNP) Testing."

ECHO and MUGA are tests obtained in radiology and nuclear medicine respectively. Both tests are commonly used in cardiology practice. MUGA, also known as radionuclide angiography, is considered the "gold standard" for monitoring cardiac function. [706] MUGA uses a radiolabeled tracer, [99]Technetium (or Tc-99m), that binds to the patients red blood cells. The cells enable an image to be visualized to track blood flow through the patient's chest, enabling the measurement of a number of functional parameters. MUGA has the advantage of high reproducibility and low inter- and intra-operator variability. However, since the use of MUGA involves infusing patients with radiolabeled substance, the routine use of this test would be impractical as repeating tests at the recommended frequency would expose patients to a considerable amount of radiation. Like ECHO, MUGA is insensitive to small changes in cardiac function.[707] For the purposes of this study, the cost and disutility associated with administration of Tc-99m was not considered. Those estimates could not be obtained as cost of the Tc-99m is facility specific and the disutility corresponding to the administration of radiation could not be found in published literature.

ECHO is a safe, non-invasive method to measure cardiac function. ECHO can provide measures of both systolic and diastolic function, and can provide more functional parameters than MUGA without exposing patients to additional radiation.[708] There are many different types of ECHO that are in routine use; however, the technology is essentially the same. Ultrasonic reflection is used to visualize the structure of the heart, the addition of Doppler technology enables the visualization of blood flow, and the

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[706] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment."

[707] Ibid.; Danias and Heller, "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction."

[708] Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure."

addition of tissue Doppler technology enables the visualization of myocardial motion[709].

ECHO is frequently used to monitor patients for cardiotoxicity; the parameters that are typically measured are left-ventricular ejection-fraction and fractional shortening. ECHO has limitations because both LVEF and FS are insensitive to small changes in cardiac function and has the disadvantage of high inter- and intra-operator variability.[710] The type of ECHO chosen for this study was a complete ECHO (CPT code 99306); see Appendix C for a full description of the procedure. The estimated costs used in this study were obtained from Medicare reimbursement amounts that are available on the CMS website (www.cms.gov). Costs for both ECHO and MUGA are likely underestimated as a significant number of patients in the cohort would have third party payers other than Medicare with a different reimbursement schedule.

6.4   Incidence of Cardiac Dysfunction

Incidence of chemotherapy-induced cardiac dysfunction has a large range of reported values. The incidence rates used in the current study were obtained from published literature; this is a major limitation of this study as these estimates are often considered low. There are several reasons why estimates from published studies would be considered low. Studies with prospective data collection that do report the number of patients with cardiac dysfunction, often only report patients that develop symptoms consistent with heart failure (often reported as NYHA Class III or IV, which would

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[709] Altena et al., "Cardiovascular Toxicity Caused by Cancer Treatment"; Vitarelli et al., "The Role of Echocardiography in the Diagnosis and Management of Heart Failure."

[710] Shan, Lincoff, and Young, "Anthracycline-Induced Cardiotoxicity"; Wu, "Cardiotoxic Drugs: Clinical Monitoring and Decision Making."

correspond to ACC/AHA late Stage C or Stage D). Studies that conduct routine screening for cardiac dysfunction as part of the study protocol, typically conduct the tests only while the patient is receiving the drug or regimen under study. Occasionally investigators will report events during a follow-up period; however, the follow-up duration may be for a year or less. Studies of chemotherapy-induced cardiac dysfunction have also included retrospective chart reviews, which is problematic because the definition of cardiac dysfunction may not be consistent. Since reporting such effects to the Adverse Event Reporting System (AERS) is voluntary at the point-of-care level, cases are missed and not included in a comprehensive database that otherwise would be considered the best source of this information

Cardiac dysfunction from breast cancer therapy can develop at any time during the recommended surveillance period, which is 15 years. In this study, point estimates for incidence were 15.4% [711] and 27% for anthracycline-based therapy and for additional trastuzumab, respectively[712]. The ranges used for sensitivity analyses varied between 10% and 20% for anthracycline therapy and 20% to 34% for patients treated with additional trastuzumab. Although the overall result of the analysis remained insensitive to changes in incidence, the trend showed increasing costs for all monitoring modalities as incidence increased, which would be expected as greater incidence would require more patients to be treated. The highest incidence rate found in published literature was 57%, which is reported in a study that did prospectively monitor patients throughout the entire

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[711] Palmeri et al., "Doxorubicin-Docetaxel Sequential Schedule: Results of Front-Line Treatment in Advanced Breast Cancer."

[712] Seidman et al., "Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience"; D. Slamon et al., "Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC-T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC-TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in HER2 Positive Early Breast Cancer Patients: BCIRG 006 Study.," *Breast Cancer Research and Treatment* 94 (December 2005): S1–S301.

surveillance period of 15 years, however because the study population was pediatric leukemia survivors, this incidence value was not used as it would not accurately represent the population in this study. [713]

6.5   Average Costs

The average costs for each strategy being compared are $10,062, $14,639, $15,656 and $13,627 for BNP, ECHO and MUGA, and No Monitoring, respectively. These total average costs include not only the costs of the tests performed but the treatment of cardiac dysfunction discovered as a result of the screening and costs of potential acute care. Even with the option of No Monitoring, the costs of developing heart failure must be accounted for. Although the average cost does not include the cost of a test, because all patients are at risk, once patients develop symptoms, it is assumed they will be treated appropriately thus accumulating treatment costs for the remainder of the surveillance period once patients report symptoms consistent with heart failure. In the current study, only direct medical costs are being considered; therefore, the lost productivity due to additional radiological exams was not accounted for. Accounting for indirect medical costs could increase average costs for both ECHO and MUGA, which would unlikely change the overall conclusion since it would merely increase the incremental cost between each alternative and BNP.

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[713] Lipshultz and Colan, "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer."

6.6   Average Effectiveness

The average effectiveness of each alternative was 6.92, 6.61, 6.49 and 4.22 QALY's for BNP, ECHO, MUGA and No Monitoring, respectively. When patients are screened with any of the test options under comparison, the average effectiveness is greater than that of doing nothing. This difference is likely because when patients are diagnosed after symptoms have manifested, the mortality is high. However, when patients are diagnosed in earlier stages of cardiac dysfunction, they are able to begin treatment that can slow disease progression, even reverse the remodeling process, and ultimately improve their prognosis.

6.7   Cost-Effectiveness

In the base-case analysis, cost-effectiveness results were $1,454, $3,226, $2,231 and $2,413 per QALY for BNP, No Monitoring, ECHO and MUGA, respectively. The cost-effectiveness results indicate that BNP would be the most attractive monitoring strategy; however the incremental cost-effectiveness is a more accurate index of comparison between alternatives to determine cost-utility. When comparing BNP to all other alternatives, each resulting ICER was -$1,322, -$14,888, -$12,964 for comparisons to No Monitoring, ECHO and MUGA, respectively. Since all resulting ICER values are less than zero, this indicates that BNP is an absolute dominant strategy over all other alternatives under comparison.

Typically, each ICER value is compared to the commonly accepted WTP threshold of $50,000 per QALY. Some argue that $50,000 is somewhat arbitrary and doesn't adequately reflect factors such as inflation. An alternative to the commonly accepted WTP of $50,000 is to use the per capita GNP multiplied by two. In the calendar

year 2010, which is the year under study, the per capita GNP is $47,800, resulting in a WTP threshold that would be approaching $100,000. If this higher WTP value was adopted in this study, the conclusions of the original analysis when comparing all strategies to BNP would not change. Alternatives can also be compared and decisions made simply on predetermined acceptable ICER values. Similar to increasing the WTP threshold, this would not change the original conclusions as ICER values for ECHO and MUGA were both negative numbers.

6.8   Sensitivity Analysis

Both one-way and probabilistic sensitivity analyses were performed. One-way sensitivity analyses tested the robustness of results over varying discount rates, disutility estimates, probability of testing positive for HER-2, incidence of cardiac dysfunction with anthracycline regimens, incidence of cardiac dysfunction with the addition of trastuzumab, and varying the probability of being diagnosed in an asymptomatic stage. The point estimates and ranges used for each variable are listed in Appendix E and full results are listed in Appendix F. Regardless of the variable under analysis, comparing BNP to all other strategies resulted in an ICER value less than zero, indicating that BNP is an absolute dominant strategy over No Monitoring, ECHO and MUGA.

Tornado diagrams were constructed for each category of variables (i.e. transition probabilities, mortality, costs, test characteristics and utilities). The variables that had the greatest effect on the results included the following: probability that patients will be diagnosed in an asymptomatic stage, the probability patients will transition from an asymptomatic stage to symptomatic stage while being treated appropriately, the probability of death in Stages A and D, BNP sensitivity and specificity, the cost of

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hospitalization and cost of office visits for established patients, and the utility estimates for hospitalization and for patients in Stages C/D. Although the ranges of these variables had the greatest effect on results, the conclusions were consistent to those in the one-way analyses; over the range that each variable was analyzed, when comparing BNP to all other alternatives, the resulting ICER values were less than zero, indicating that BNP was an absolute dominant strategy over No Monitoring, ECHO and MUGA.

A probabilistic sensitivity analysis was performed via a Monte Carlo simulation with 10,000 iterations. Distributions were created for all variables. The resulting average costs were $6,441, $12,209, $13,159 and $14,208 and the average effectiveness estimates were 8.719, 8.312, 8.241, and 4.265 for BNP, ECHO, MUGA and No Monitoring, respectively. When comparing all options to BNP, each alternative has a higher cost and lower effectiveness, giving negative ICER values for each strategy. Thus, the probabilistic sensitivity analysis further supports the use of BNP to monitor for cardiac dysfunction is breast cancer patients.

6.9   Study Limitations

The biggest limitation of this study is that the transition probabilities were obtained from published literature. Sources of estimates were studies of all types and each has its own inherent limitations. The majority of literature using BNP is cardiology literature, not oncology, and in these studies BNP may be used in a variety of settings such as screening, diagnosis, monitor treatment effectiveness, and prediction of long-term outcomes. Oncology literature that does discuss the use of BNP typically involves proposing its use, not in scenarios where it has already been used. While there is oncology literature describing the use of ECHO and MUGA; studies typically describe

their use in pre-treatment assessment of cardiac function, as well as assessing cardiac function through the duration of treatment.

All disease state transitions were obtained from cardiology literature including annual risk of mortality, transitions from asymptomatic dysfunction to symptomatic dysfunction, probability of being diagnosed in an asymptomatic stage, probabilities of hospitalization and ED visits, and the probability of readmission. It has been suggested that the prognosis of heart failure from chemotherapy is worse than heart failure of other etiologies; however, stage-specific estimates have not been made. Since cardiac dysfunction is rarely discovered prior to cancer patients experiencing symptoms, cancer-specific transitions from asymptomatic dysfunction to symptomatic dysfunction would be difficult to obtain. As outlined in Chapter Two, there are many other cancer therapies that can cause cardiotoxicity. This study only considered the use of anthracyclines and trastuzumab, which could be considered another limitation.

The subjects in the hypothetical cohort are assumed to have no evidence of heart disease, are in complete remission from breast cancer and do not possess any risk factors other than exposure to cardiotoxic cancer therapy. It is also assumed that there are no patients that are lost to follow-up; the only exit from the model is death. The lack of consideration for patients lost to follow-up is not a realistic representation of current ambulatory practice. Additionally, the only source of mortality included in this study is that from the progression of heart failure, thus mortality from breast cancer recurrence and age-specific mortality is considered the same across all monitoring strategies.

The utility estimates were from studies of heart failure patients; these estimates are for heart failure patients without mention of past medical history. This cohort has a past medical history of invasive breast cancer. An assumption had to be made that all patients are starting with a utility estimate in Stage A, which was given a value of 1.0.

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Since there is an underlying assumption that patients do not possess any comorbid conditions that could potentially confound disease progression or mortality, and there would likely be a disutility estimate associated with a past medical history of cancer, this initial utility estimate is likely high.

Most cost estimates used in this study are Medicare reimbursement amounts for the calendar year 2010 and were obtained from the CMS website. The one exception was the cost of medications, which were obtained from the Texas Medicaid website. The ages of breast cancer survivors can range anywhere from 20 years and up. This study makes the assumption that all patients are monitored with the same frequency regardless of their age. Test costs were obtained from Medicate reimbursement amounts. For other payers this would be an underestimation of test costs, although since the median age of diagnosis for breast cancer is 61 years; this would be an accurate representation for the majority of patients in the study population.

However, in reality, monitoring is more likely to be conducted in younger patients who were diagnosed with aggressive disease requiring received higher doses of anthracyclines and/or additional cycles. Therefore test costs in this study could potentially be underestimated. Medication costs were determined with the assumption that all patients would receive optimal treatment as recommended by heart failure treatment and management practice guidelines. In reality, these guidelines would not likely be followed by all prescribers. This would ultimately lead to lower overall medication costs but a potential increase in the probability of acute care, subsequently leading to an increase in emergency department and hospitalization costs.

Medication costs were obtained from Texas Medicaid and were the median values for the Maximum Allowable Charge (MAC). These costs may be higher for some medications that are potentially on discount lists for some pharmacies (i.e. Wal-Mart®

$4/30-day supply / $10 / 90-day supply) which would lead to zero cost to the third party payer for those respective medications. The Wal-Mart list includes the following medications that would affect the total treatment costs relevant to this study: carvedilol 25mg tablets, lisinopril 20mg tablets, spironolactone 25mg tablets, hydralazine 25mg tablets, furosemide 40mg tablets, and isosorbide mononitrate 30mg ER and 60mg ER tablets. Although using some of the medications from this list decreases the cost to the payer, it increases the tablet burden for patients; likely affecting medication compliance and ultimately increase costs for acute care and mortality.

Additionally, it was assumed that patients with a positive result from BNP would receive confirmation with ECHO. This assumption has a number of implications. The false positive rate for anthracyclines and trastuzumab is 0.22 and 0.19 respectively which would lead to a high overall cost for additional testing with ECHO. In actual practice the need for confirmatory testing would likely only be required in patients that showed a significant increase from their baseline BNP level ($> 30\%$ from baseline) that was below what would be considered a positive result (i.e. < 100 ng/mL). An additional implication of this assumption is the assumption that the ECHO would recognize that initial result as false positive, thus that patient would not receive heart failure treatment. In this study, when a confirmatory test is used, it doesn't take into account the test characteristics of ECHO, it is automatically assumed that it will produce the correct result. Although utilization of a confirmatory test can potentially introduce "work-up" bias, use of the confirmatory test was chosen because published studies in screening cardiology patients included ECHO as a confirmatory test. It has been shown that both either left-ventricular ejection fraction and fractional shortening have low sensitivity in detecting small changes in cardiac function, thus using a test of LVEF for confirmation may not be appropriate in this setting.

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6.10 Conclusions and Directions for Further research

Research should be conducted to obtain estimates from cancer patients who have developed cardiac dysfunction subsequent to their therapy. Those studies would include attaining more accurate incidence estimates of cardiac dysfunction resulting from the use of anthracycline-based chemotherapy or trastuzumab. One way to obtain such data could include the development of policy that would create a practice-level or point-of-care protocol making reporting these effects to the FDA via the AERS reporting system required in this practice setting. Additional estimates of interest would include cancer-specific estimates of treatment costs, disease progression, utilities and mortality.

This study provides compelling evidence that BNP has potential utility in monitoring breast cancer for the development of cardiac dysfunction. The results of cost-effectiveness analysis show that the incremental cost-effectiveness of BNP when compared to ECHO, MUGA, or No Monitoring, makes it an attractive choice. The probabilistic sensitivity analysis provides additional evidence as the results were confirmed to be insensitive to varying estimates for all included variables. As previously mentioned, the cost estimates used in this study are likely lower than one would expect in an actual breast cancer patient population, so it is unknown if more accurate cost estimates in the population of interest would change the results of the current study.

Monitoring for cardiotoxicity in breast cancer patients needs to be conducted after completion of chemotherapy as well as during the course of treatment. The recommended frequency at which is required in this patient population, would ideally employ a strategy that has a low cost and the absence of any additional time commitment, both of these qualities make BNP a compelling option when compared to alternative strategies. Results of this study not only show that BNP is a cost-effective alternative, these results show

that the utilization of BNP has a lower cost and greater effectiveness of not monitoring at all, which is the most compelling reason to consider its implementation into current routine surveillance practice.

APPENDIX A: CHEMOTHERAPY REGIMEN ABBREVIATIONS[714]

Abb.	Regimen
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
AC	Doxorubicin, Cyclophosphamide
TC	Docetaxel, Cyclophosphamide
FAC/CAF	Fluorouracil, Doxorubicin, Cyclophosphamide
FEC/CEF	Fluorouracil, Epirubicin, Cyclophosphamide
CMF	Cyclophosphamide, Methotrexate, Fluorouracil
EC	Epirubicin, Cyclophosphamide
AC→TH	Doxorubicin, Cyclophosphamide → Docetaxel/Paclitaxel and Trastuzumab
TCH	Docetaxel/Paclitaxel, Carboplatin and Trastuzumab
TH→FEC	Docetaxel/Paclitaxel and Trastuzumab → Fluorouracil, Epirubicin, Cyclophosphamide

Abb.: Abbreviation

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[714] NCCN Breast Cancer Panel Members, "Breast Cancer Practice Guidelines V2.2011."

APPENDIX B: CHEMOTHERAPY REGIMENS AND SCHEDULES[715]

Regimen	Drugs	Dose (mg/m²)	When Given	Cycle Length	# of Cycles
TAC	Docetaxel	75	Day 1	21 Days	6
	Doxorubicin	50			
	Cyclophosphamide	500			
	With Filgrastim Support				
Dose-Dense AC →Paclitaxel	Doxorubicin	60	Day 1	14 Days	4
	Cyclophosphamide	600			
	Followed By:				
	Paclitaxel - 3 Hr Infusion	175	Day 1	14 Days	4
	With Filgrastim Support				
±	Trastuzumab	4	With 1st dose of Paclitaxel		
followed by:	Trastuzumab	2	Weekly for 1 year		
or	Trastuzumab	6	Every 3 weeks for 1 year		
AC →Paclitaxel	Doxorubicin	60	Day 1	21 Days	4
	Cyclophosphamide	600			
	Followed By:				
	Paclitaxel - 1 Hr Infusion	80		Weekly	12
±	Trastuzumab	4	With 1st dose of Paclitaxel	One Dose	
followed by:	Trastuzumab	2	Weekly		For 1 Yr.
or	Trastuzumab	6	Every 3 weeks		For 1 Yr.

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[715] Ibid.

Regimen	Drugs	Dose (mg/m^2)	When Given	Cycle Length	# of Cycles
AC	Doxorubicin	60 mg/ m2	Day 1	21 Days	4
	Cyclophosphamide	600 mg/ m2			
EC	Epirubicin	100 mg/m2	Day 1	21 Days	8
	Cyclophosphamide	830 mg/m2			
Dose-Dense A-T-C	Doxorubicin	60 mg/ m2	Day 1	14 days	4
	Followed by:				
	Paclitaxel - 3 Hr Infusion	175 mg/m2	Day 1	14 days	4
	Followed by:				
	Cyclophosphamide	600 mg/ m2	Day 1	14 days	4
	With Filgrastim Support				
FEC →Docetaxel	5-Fluorouracil	500 mg/m2	Day 1	21 Days	3
	Epirubicin	100 mg/m2			
	Cyclophosphamide	500 mg/m2			
	Followed by:				
	Docetaxel	100 mg/m2	Day 1	21 Days	3

Regimen	Drugs	Dose (mg/m^2)	When Given	Cycle Length	# of Cycles
FEC →Weekly Paclitaxel	5-Fluorouracil	600	Day 1	21 Days	4
	Epirubicin	90			
	Cyclophosphamide	600			
	Followed by 3 weeks with No Treatment				
	Followed by:				
	Paclitaxel	100		Weekly	8
FAC	5-Fluorouracil	500	1&8 or 1&4	21 Days	6
	Doxorubicin - 72 hr infusion	50	Day 1		
	Cyclophosphamide	500			
CAF	Cyclophosphamide (P.O.)	100	1 to 14	28 Days	6
	Doxorubicin	30	1&8		
	5-Fluorouracil	500	1&8		
CEF	Cyclophosphamide (P.O.)	75	1 to 14	28 Days	6
	Epirubicin	60	1&8		
	5-Fluorouracil	500	1&8		
	With Cotrimoxazole Support				
CMF	Cyclophosphamide (P.O.)	100	1 to 14	28 Days	6
	Methotrexate	40	1&8		
	5-Fluorouracil	600	1&8		

Regimen	Drugs	Dose (mg/m^2)	When Given	Cycle Length	# of Cycles
CMF	Cyclophosphamide (P.O.)	100	1 to 14	28 Days	6
	Methotrexate	40	1&8		
	5-Fluorouracil	600	1&8		
AC →Docetaxel	Doxorubicin	60	Day 1	21 Days	4
	Cyclophosphamide	600			
	Followed By:				
	Docetaxel	100	Day 1	21 days	4
TCH	Docetaxel	75	Day 1	21 Days	6
	Carboplatin	AUC 6			
	Trastuzumab	4 mg/kg	Week 1		
Followed By:	Trastuzumab	2 mg/kg	Week 2	Weekly	17
Followed By:	Trastuzumab	6 mg/kg	Week 18	Every 3 Weeks	QS to 1 Yr.

APPENDIX C: FULL MEDICARE DESCRIPTIONS OF RADIOLOGY PROCEDURES

Table C.1 MUGA CPT Codes and Procedure Descriptions

Code	Description
78472	Cardiac blood pool imaging, gated equilibrium; planar, single study at rest or stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without additional quantitative processing
78473	Cardiac blood pool imaging, gated equilibrium; multiple studies, wall motion study plus ejection fraction, at rest and stress (exercise and/or pharmacologic), with or without additional quantification
78481	Cardiac blood pool imaging (planar), first pass technique; single study, at rest or with stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without quantification
78483	Cardiac blood pool imaging (planar), first pass technique; multiple studies, at rest and with stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without quantification
78494	Cardiac blood pool imaging, gated equilibrium, SPECT, at rest, wall motion study plus ejection fraction, with or without quantitative processing
78496	Cardiac blood pool imaging, gated equilibrium, single study, at rest, with right ventricular ejection fraction by first pass technique (List separately in addition to code for primary procedure)

Table C.2 ECHO CPT Codes and Procedure Descriptions

Code	Description
93306	Echocardiography, transthoracic, real-time with image documentation (2D) includes M-mode recording, when performed, complete, with spectral Doppler echocardiography, and with color flow Doppler echocardiography
93307	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography
93308	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study
93312	Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); including probe placement, image acquisition, interpretation and report
93313	Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); placement of transesophageal probe only
93314	Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); image acquisition, interpretation and report only

APPENDIX D: VARIABLE DEFINITIONS

Variable	Definition
BNP_Sensitivity	Sensitivity of BNP Test
BNP_Specificity	Specificity of BNP Test
ECHO_Sensitivity	Sensitivity of Echocardiogram
ECHO_Specificity	Specificity of Echocardiogram
MUGA_Sensitivity	Sensitivity of Multi-gated Acquisition Scan
MUGA_Specificity	Specificity of Multi-gated Acquisition Scan
DR	Discount Rate
Incidence_AC	Incidence of cardiac dysfunction in patients who have received an anthracycline-based regimen
Incidence_T	Incidence of cardiac dysfunction in patients who have received treatment with Trastuzumab
C_acutecare	Cost of Acute Care
C_BNP	Cost of BNP
C_Confirm	Cost of Confirmation Testing
C_ECHO	Cost of Echocardiogram
C_ED	Cost of Emergency Department Visit
C_Hosp	Cost of Hospitalization
C_meds_asx	Cost of Medications to Treat Heart Failure in Asymptomatic Stage
C_meds_sx	Cost of Medications to Treat Heart Failure in Symptomatic Stages
C_MM	Cost of Medication Management
C_muga	Cost of Multi-gated Acquisition Scan

Variable Definitions Continued

C_office_est	Cost of Office Visit for Established Patient
C_office_new	Cost of Office Visit for New Patient
C_outpt_B	Total Cost of Outpatient Management in Stage B
C_outpt_CD	Total Cost of Outpatient Management in Stages C and D
P_asxtosx_Tx	Probability of Transitioning from an asymptomatic to symptomatic stage while being treated appropriately
P_asxtosx_NoTx	Probability of Transitioning from an asymptomatic to symptomatic stage without being treated appropriately
P_ED	Probability of an Emergency Department Visit
P_death_A	Probability of Death in Stage A
P_death_B	Probability of Death in Stage B
P_death_C	Probability of Death in Stage C
P_death_D	Probability of Death in Stage D
P_death_Hosp	Probability of Death While Hospitalized
P_death_postDC	Probability of Death in the Year After Being Hospitalized
P_Hosp	Probability of Hospitalization
P_Readmit	Probability of Readmission
U_StageA	Utility Estimate for Patients in Stage A
U_StageB	Utility Estimate for Patients in Stage B
U_StageCD	Utility Estimate for Patients in Stages C and D
U_Hosp	Utility Estimate for Hospitalized Patients
U_Disutil	Disutility Estimate Accounting for Additional Time Required for Testing

APPENDIX E: SUMMARY OF MODEL INPUTS AND RANGES FOR SENSITIVITY ANALYSES

Table E.1 Incidence Variables, Mortality and Transition Probabilities

Parameter	Base Case	Low	High
DR	0.030	0.000	0.050
P_HER-2[1]	0.250	0.200	0.300
Incidence_AC[3]	0.154	0.100	0.200
Incidence_T[3]	0.270	0.200	0.340
P_ASXtoSX_TX[1]	0.065	0.050	0.100
P_ASXtoSX_NoTX[1]	0.098	0.050	0.150
P_Death_A[2]	0.006	0.002	0.012
P_Death_B[2]	0.008	0.005	0.012
P_Death_C[2]	0.056	0.043	0.072
P_Death_D[2]	0.275	0.113	0.316
P_Death_Hosp[3]	0.062	0.056	0.068
P_Death_postDC[2]	0.22	0.162	0.312
P_Diag_ASX[3]	0.795	0.716	0.875
P_ED[3]	0.042	0.038	0.046
P_Hosp[3]	0.209	0.188	0.230
P_Readmit[1]	0.269	0.196	0.370

[1] Range represents that of the original cited source as high and low values
[2] Range represents that of the original cited source as 95% CI
[3] Estimated ranges   (± 10% of point estimate)

Table E.2 Test Characteristics

		Sensitivity			Specificity		
		Base Case	Low	High	Base Case	Low	High
Test	**BNP**[1]	0.93	0.91	0.95	0.74	0.63	0.83
	ECHO[2]	0.64	0.62	0.66	0.81	0.75	0.87
	MUGA[2]	0.90	0.88	0.92	0.72	0.65	0.79

[1] Ranges from original cited source reported as 95% CI [2] Estimated Range

Table E.3 Utility Estimates

Parameter	Base Case	Low	High
U_BNP_A	1.000	-	-
U_BNP_B[1,3]	0.865	0.852	0.877
U_BNP_CD[1,3]	0.710	0.624	0.795
U_Hosp[1]	0.520	0.480	0.800
U_disutil[2]	0.025	0.020	0.030

[1] Range used is reported range from point estimate cited source
[2] Published Range [3] Specified 95% CI [4] Estimated disutility and range

Table E.4 Cost Inputs for Base-Case and Sensitivity Analyses

Parameter	Base Case ($)	Low ($)	High ($)
C_BNP[1]	48	40	58
C_ECHO	393	265	522
c_MUGA	464	372	500
C_confirm[2]	393	0	393
C_meds_ASX[3]	226	206	407
C_meds_SX[3]	1,162	1,039	1,285
C_MM[4]	63	57	69
C_office_est[5]	70	27	117
C_office_new[5]	110	81	137
C_ED[5]	130	68	191
C_hosp[5]	6,676	4,235	9,609

Costs are in 2010 U.S. Dollars; codes
[1] Base-case estimates is the 2010 Medicare reimbursement for natriuretic peptides,
 range is from previously published estimates of test costs adjusted to 2010 U.S. dollars;
[2] Base-case estimates is cost of ECHO, range accounts for the possibility that not all positives
 will require confirmatory testing – only results with BNP level in "grey area;"
[3] High and low values represent the possible range for chosen medications obtained
 TX Medicaid Drug Costs; [4] Estimated range; [5] Range represents high and low values from
 Medicare Reimbursement for corresponding CPT or DRG

APPENDIX F: FULL RESULTS FROM ONE-WAY SENSITIVITY ANALYSES

Table F.1 One-Way Sensitivity Analysis of Cost-Effectiveness with Varying Discount Rate

DR	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	I.C. ($)	I.E. (QALY)	ICER ($/QALY)
0.00	BNP	10,822.69	7.908	1,368.60	-	-	-
0.00	No Monitoring	14,238.46	4.571	3,114.66	3,415.77	-3.336	-1,023.78
0.00	ECHO	15,823.64	7.582	2,087.02	5,000.95	-0.326	-15,343.81
0.00	MUGA	16,770.41	7.436	2,255.38	5,947.72	-0.472	-12,597.83
0.03	BNP	10,062.37	6.920	1,454.04	-	-	-
0.03	No Monitoring	13,627.34	4.224	3,226.48	3564.96	-2.697	-1,321.98
0.03	ECHO	14,739.36	6.606	2,231.16	4676.98	-0.314	-14,888.06
0.03	MUGA	15,655.56	6.489	2,412.70	5593.19	-0.431	-12,963.52
0.05	BNP	9,656.12	6.385	1,512.35	-	-	-
0.05	No Monitoring	13,287.12	4.026	3,300.26	3,631.00	-2.359	-1,539.37
0.05	ECHO	14,146.89	6.079	2,327.35	4,490.78	-0.306	-14,661.27
0.05	MUGA	15,043.99	5.977	2,517.19	5,387.88	-0.408	-13,194.53

DR: Discount Rate; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness;
I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio

Table F.2 One-Way Sensitivity Analysis of HER-2 Probability

HER-2 %	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	I.C. ($)	I.E. (QALY)	ICER ($/QALY)
0.20	BNP	10,006.97	6.988	1,432.05	-	-	-
0.20	No Monitoring	13,627.34	4.224	3,226.48	3,620.36	-2.764	-1,309.71
0.20	ECHO	14,730.63	6.670	2,208.55	4,723.66	-0.318	-14,853.40
0.20	MUGA	15,664.79	6.554	2,390.09	5,657.81	-0.434	-13,042.49
0.25	BNP	10,062.37	6.920	1,454.04	-	-	-
0.25	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.25	ECHO	14,739.36	6.606	2,231.16	4,676.98	-0.314	-14,888.06
0.25	MUGA	15,655.56	6.489	2,412.69	5,593.19	-0.431	-12,963.53
0.30	BNP	10,117.77	6.853	1,476.46	-	-	-
0.30	No Monitoring	13,627.34	4.224	3,226.48	3,509.57	-2.629	-1,334.88
0.30	ECHO	14,748.08	6.542	2,254.21	4,630.31	-0.310	-14,923.59
0.30	MUGA	15,646.34	6.424	2,435.75	5,528.56	-0.429	-12,883.70

HER-2%: Probability of Testing Positive for HER-2 Overexpression; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness; I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio

Table F.3 One-Way Sensitivity Analysis of Varying Incidence Estimates from Anthracycline-Only Regimens

Incidence_AC	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	IC ($)	IE (QALY)	ICER ($/QALY)
0.100	BNP	9,064.52	7.679	1,180.43	-	-	-
0.100	No Monitoring	13,627.34	4.224	3,226.48	4,562.82	-3.455	-1,320.48
0.100	ECHO	14,222.99	7.321	1,942.68	5,158.47	-0.358	-14,421.46
0.100	MUGA	15,309.33	7.223	2,119.61	6,244.82	-0.456	-13,685.62
0.154	BNP	10,062.37	6.920	1454.04	-	-	-
0.154	No Monitoring	13,627.34	4.224	3226.48	3564.96	-2.697	-1,321.98
0.154	ECHO	14,739.36	6.606	2231.16	4676.98	-0.314	-14,888.06
0.154	MUGA	1,5655.56	6.489	2412.70	5593.19	-0.431	-12,963.52
0.200	BNP	10,531.91	6.439	1,635.54	-	-	-
0.200	No Monitoring	13,627.34	4.224	3,226.48	3,095.43	-2.216	-1,396.98
0.200	ECHO	14,889.99	6.153	2,420.09	4,358.08	-0.287	-15,199.34
0.200	MUGA	15,685.53	6.024	2,603.75	5,153.62	-0.415	-12,412.90

Incidence_AC: Incidence of Cardiac Dysfunction in Patients who Received Anthracycline-Based Chemotherapy; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness; I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio

Table F.4 One-Way Sensitivity Analysis of Varying Incidence Estimates for Trastuzumab Regimens

Incidence_T	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	I.C. ($)	I.E. (QALY)	ICER (I.C./I.E.)
0.20	BNP	9,941.89	7.098	1,400.70	-	-	-
0.20	No Monitoring	13,627.34	4.224	3,226.48	3,685.45	-2.874	-1,282.25
0.20	ECHO	14,745.94	6.773	2,177.03	4,804.05	-0.324	-14,809.88
0.20	MUGA	15,711.68	6.660	2,359.10	5,769.79	-0.438	-13,180.69
0.27	BNP	10,062.37	6.920	1,454.04	-	-	-
0.27	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.27	ECHO	14,739.36	6.606	2,231.16	4,676.98	-0.314	-14,888.06
0.27	MUGA	15,655.56	6.489	2,412.69	5,593.19	-0.431	-12,963.53
0.34	BNP	10,113.39	6.796	1,488.08	-	-	-
0.34	No Monitoring	13,627.34	4.224	3,226.48	3,513.95	-2.573	-1,365.88
0.34	ECHO	14,691.17	6.490	2,263.80	4,577.78	-0.307	-14,928.03
0.34	MUGA	15,568.60	6.370	2,444.24	5,455.21	-0.427	-12,782.95

Incidence_T: Incidence of Cardiac Dysfunction in Patients who Received Additional Treatment with Trastuzumab; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness; I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio

Table F.5 One-Way Sensitivity Analysis of Varying Probability Estimates of Diagnosis Without Symptoms

P_Diag_ASX	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	I.C. ($)	I.E. (QALY)	ICER (I.C. /I.E.)
0.716	BNP	10,066.56	6.842	1,471.35	-	-	-
0.716	No Monitoring	13,627.34	4.224	3,226.48	3,560.78	-2.618	-1,360.06
0.716	ECHO	14,743.91	6.533	2,256.68	4,677.35	-0.308	-15,174.30
0.716	MUGA	15,659.78	6.413	2,442.02	5,593.23	-0.429	-13,035.47
0.795	BNP	10,062.37	6.920	1,454.04	-	-	-
0.795	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.795	ECHO	14,739.36	6.606	2,231.16	4,676.98	-0.314	-14,888.10
0.795	MUGA	15,655.56	6.489	2,412.69	5,593.19	-0.431	-12,963.50
0.875	BNP	10,058.13	7.000	1,436.90	-	-	-
0.875	No Monitoring	13,627.34	4.224	3,226.48	3,569.21	-2.776	-1,326.68
0.875	ECHO	14,734.74	6.680	2,205.88	4,676.61	-0.320	-14,608.95
0.875	MUGA	15,651.29	6.566	2,383.69	5,593.15	-0.434	-12,891.48

P_Diag_ASX: Probability of Patients Being Diagnosed with Cardiac Dysfunction in an Asymptomatic Stage; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness; I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio

Table F.6 One-Way Sensitivity Analysis of Varying the Disutility Estimate

U_disutil	STRATEGY	COST ($)	EFF (QALY)	CE ($/QALY)	I.C. ($)	I.E. (QALY)	ICER (I.C./I.E.)
0.020	BNP	10,062.37	6.920	1,454.04	-	-	-
0.020	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.020	ECHO	14,739.36	6.697	2,201.05	4,676.98	-0.224	-20,900.70
0.020	MUGA	15,655.56	6.578	2,380.04	5,593.19	-0.342	-16,333.60
0.025	BNP	10,062.37	6.920	1,454.04	-	-	-
0.025	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.025	ECHO	14,739.36	6.606	2,231.16	4,676.98	-0.314	-14,888.10
0.025	MUGA	15,655.56	6.489	2,412.69	5,593.19	-0.431	-12,963.50
0.030	BNP	10,062.37	6.920	1,454.04	-	-	-
0.030	No Monitoring	13,627.34	4.224	3,226.48	3,564.96	-2.697	-1,321.98
0.030	ECHO	14,739.36	6.516	2,262.10	4,676.98	-0.405	-11,562.00
0.030	MUGA	15,655.56	6.400	2,446.26	5,593.19	-0.520	-10,746.30

U_Disutil: Disutility Estimate Associated with Additional Required Testing; Costs in 2010 U.S. Dollars; Eff: Effectiveness in QALY, CE: Cost-Effectiveness [Cost/Eff]; I.C.: Incremental Cost; I.E.: Incremental Effectiveness; ICER: Incremental Cost-Effectiveness Ratio [I.C/I.E.]

APPENDIX G STAGE AND CUMULATIVE COSTS FOR EACH STRATEGY

Table G.1 BNP Stage and Cumulative Costs and Effectiveness

	HER-2 Positive				HER-2 Negative			
	S.C. ($)	C.C. ($)	S.E. (QALY)	C.E. (QALY)	S.C. ($)	C.C. ($)	S.E. (QALY)	C.E. (QALY)
0	$192.00	$192.00	0.500	0.500	$192.00	$192.00	0.500	0.500
1	$902.36	$1,094.36	0.958	1.458	$636.65	$828.65	0.961	1.461
2	$1,238.16	$2,332.52	0.866	2.324	$864.49	$1,693.14	0.894	2.355
3	$1,341.69	$3,674.21	0.750	3.074	$975.63	$2,668.77	0.810	3.164
4	$1,279.88	$4,954.09	0.630	3.704	$961.37	$3,630.14	0.719	3.883
5	$1,172.56	$6,126.65	0.516	4.220	$943.72	$4,573.87	0.629	4.512
6	$1,022.42	$7,149.07	0.416	4.636	$876.57	$5,450.43	0.544	5.056
7	$870.25	$8,019.32	0.330	4.966	$806.69	$6,257.12	0.465	5.521
8	$723.49	$8,742.81	0.259	5.225	$727.26	$6,984.38	0.395	5.916
9	$590.53	$9,333.34	0.201	5.426	$645.53	$7,629.91	0.334	6.250
10	$474.95	$9,808.29	0.155	5.580	$566.14	$8,196.05	0.280	6.530
11	$377.40	$10,185.70	0.118	5.698	$491.84	$8,687.89	0.235	6.765
12	$296.87	$10,482.57	0.090	5.788	$424.08	$9,111.96	0.196	6.961
13	$231.53	$10,714.10	0.068	5.856	$363.45	$9,475.41	0.163	7.123
14	$179.25	$10,893.35	0.051	5.907	$309.97	$9,785.38	0.135	7.258
15	-	$10,893.35	-	5.907	-	$9,785.38	-	7.258

S.C.: Stage Costs; C.C.: Cumulative Cost; S.E.: Stage Effectiveness; C.E.: Cumulative Effectiveness

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Table G.2 ECHO Stage and Cumulative Costs and Effectiveness

	HER-2 (+)				HER-2 (-)			
Stage	S.C. ($)	C.C ($)	S.E. (QALY)	C.E. (QALY)	S.C. ($)	C.C ($)	S.E. (QALY)	C.E. (QALY)
0	$1,572.00	$1,572.00	0.450	0.450	$1,572.00	$1,572.00	0.450	0.450
1	$1,730.86	$3,302.86	0.852	1.302	$1,639.00	$3,211.00	0.859	1.309
2	$1,858.64	$5,161.50	0.786	2.088	$1,705.95	$4,916.95	0.807	2.117
3	$1,818.95	$6,980.45	0.690	2.778	$1,684.31	$6,601.26	0.737	2.854
4	$1,449.37	$8,429.82	0.619	3.398	$1,226.38	$7,827.64	0.696	3.550
5	$1,316.17	$9,745.99	0.512	3.909	$1,172.72	$9,000.36	0.611	4.161
6	$1,092.44	$10,838.42	0.426	4.335	$962.87	$9,963.24	0.544	4.705
7	$933.04	$11,771.46	0.339	4.675	$884.16	$10,847.40	0.467	5.172
8	$777.64	$12,549.10	0.267	4.942	$795.69	$11,643.09	0.398	5.569
9	$635.95	$13,185.05	0.208	5.150	$705.23	$12,348.32	0.336	5.906
10	$512.25	$13,697.30	0.161	5.310	$617.69	$12,966.01	0.283	6.189
11	$407.53	$14,104.83	0.123	5.433	$536.00	$13,502.02	0.237	6.426
12	$320.89	$14,425.72	0.094	5.527	$461.67	$13,963.68	0.198	6.623
13	$250.46	$14,676.19	0.071	5.598	$395.27	$14,358.95	0.165	6.788
14	$194.04	$14,870.22	0.053	5.651	$336.78	$14,695.73	0.137	6.925
15	-	$14,870.22	-	5.651	-	$14,695.73	-	6.925

S.C.: Stage Costs; C.C.: Cumulative Cost; S.E.: Stage Effectiveness; C.E.: Cumulative Effectiveness

Table G.3 MUGA Stage and Cumulative Costs and Effectiveness

Stage	HER-2 (+)				HER-2 (-)			
	S.C. ($)	C.C. ($)	S.E. (QALY)	C.E. (QALY)	S.C. ($)	C.C. ($)	S.E. (QALY)	C.E. (QALY)
0	$1,856.00	$1,856.00	0.450	0.450	$1,856.00	$1,856.00	0.450	0.450
1	$2,025.19	$3,881.19	0.860	1.310	$1,924.63	$3,780.63	0.864	1.314
2	$2,034.16	$5,915.35	0.779	2.090	$1,918.81	$5,699.44	0.804	2.118
3	$1,906.40	$7,821.75	0.676	2.765	$1,838.57	$7,538.01	0.729	2.847
4	$1,467.70	$9,289.45	0.600	3.365	$1,290.82	$8,828.83	0.684	3.531
5	$1,307.18	$10,596.62	0.492	3.857	$1,213.94	$10,042.77	0.598	4.129
6	$1,066.10	$11,662.72	0.407	4.264	$972.55	$11,015.32	0.531	4.661
7	$902.30	$12,565.02	0.323	4.588	$885.74	$11,901.06	0.455	5.115
8	$747.00	$13,312.02	0.254	4.841	$792.31	$12,693.37	0.387	5.502
9	$607.78	$13,919.80	0.197	5.038	$699.02	$13,392.39	0.326	5.828
10	$487.61	$14,407.41	0.152	5.190	$610.08	$14,002.48	0.274	6.103
11	$386.68	$14,794.09	0.116	5.306	$527.92	$14,530.40	0.230	6.332
12	$303.67	$15,097.76	0.088	5.394	$453.69	$14,984.08	0.191	6.524
13	$236.51	$15,334.27	0.066	5.461	$387.73	$15,371.82	0.159	6.683
14	$182.89	$15,517.16	0.050	5.511	$329.88	$15,701.70	0.132	6.815
15	-	$15,517.16	-	5.511	-	$15,701.70	-	6.815

S.C.: Stage Costs; C.C.: Cumulative Cost; S.E.: Stage Effectiveness; C.E.: Cumulative Effectiveness

REFERENCES:

Aaronson, Keith D., J. Sanford Schwartz, Tze-Ming Chen, Kar-Lai Wong, James E. Goin, and Donna M. Mancini. "Development and Prospective Validation of a Clinical Index to Predict Survival in Ambulatory Patients Referred for Cardiac Transplant Evaluation." *Circulation* 95, no. 12 (June 17, 1997): 2660 –2667.

Aas, I. H. Monrad. "Guidelines for Rating Global Assessment of Functioning (GAF)." *Annals of General Psychiatry* 10, no. 2 (2011). http://www.ncbi.nlm.nih.gov/pubmed/21251305.

Abassi, Zaid, Tony Karram, Samer Ellaham, Joseph Winaver, and Aaron Hoffman. "Implications of the Natriuretic Peptide System in the Pathogenesis of Heart Failure: Diagnostic and Therapeutic Importance." *Pharmacology & Therapeutics* 102, no. 3 (June 2004): 223–241.

Abeloff, Martin, Antonio Wolff, Barbara Weber, Tal Zaks, Vergilio Sacchini, and Beryl McCormick. "Cancer of the Breast." In *Abeloff: Abeloff's Clinical Oncology*, Chapter 95. Philadelphia: Churchill Livingstone/Elsevier, 2008. http://www.mdconsult.com.ezproxy.lib.utexas.edu/.

Abernethy, Amy P., Tania Shelby-James, Belinda S. Fazekas, David Woods, and David C. Currow. "The Australia-modified Karnofsky Performance Status (AKPS) Scale: a Revised Scale for Contemporary Palliative Care Clinical Practice." *BMC Palliat Care* 4, no. 7 (2005): 4–7.

Altena, Renske, Patrick J Perik, Dirk J van Veldhuisen, Elisabeth GE de Vries, and Jourik A Gietema. "Cardiovascular Toxicity Caused by Cancer Treatment: Strategies for Early Detection." *The Lancet Oncology* 10, no. 4 (April 2009): 391–399.

American College of Radiology. "BI-RADS® – Mammography, Fourth Edition." Professional Organization. *American College of Radiology*, 2003. http://www.acr.org/

Ammar, Khawaja Afzal, Steven J Jacobsen, Douglas W Mahoney, Jan A Kors, Margaret M Redfield, John C Burnett, and Richard J Rodeheffer. "Prevalence and Prognostic Significance of Heart Failure Stages: Application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the Community." *Circulation* 115, no. 12 (March 27, 2007): 1563–1570.

Ando, M, Y Ando, Y Hasegawa, K Shimokata, H Minami, K Wakai, Y Ohno, and S Sakai. "Prognostic Value of Performance Status Assessed by Patients Themselves, Nurses, and Oncologists in Advanced Non-small Cell Lung Cancer." *British Journal of Cancer* 85, no. 11 (November 2001): 1634–1639.

Armstrong, Katrina, Andrea Eisen, and Barbara Weber. "Assessing the Risk of Breast Cancer." *The New England Journal of Medicine* 342, no. 8 (February 24, 2000): 564–571.

Atkinson, Arthur J., Wayne A. Colburn, Victor G. DeGruttola, David L. DeMets, Gregory J. Downing, Daniel F. Hoth, John A. Oates, et al. "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework." *Clinical Pharmacology & Therapeutics* 69, no. 3 (March 2001): 89–95.

Auerbach, Andrew D., Mary Beth Hamel, Roger B. Davis, Alfred F. Connors, Carol Regueiro, Norman Desbiens, Lee Goldman, et al. "Resource Use and Survival of Patients Hospitalized with Congestive Heart Failure: Differences in Care by Specialty of the Attending Physician." *Annals of Internal Medicine* 132, no. 3 (February 1, 2000): 191 – 200.

Augoustides, John G.T., and Hynek Riha. "Recent Progress in Heart Failure Treatment and Heart Transplantation." *Journal of Cardiothoracic and Vascular Anesthesia* 23, no. 5 (October 2009): 738–748.

Aviles, Jennifer M., and Ronnier J. Aviles. "Advances in Cardiac Biomarkers." *Emergency Medicine Clinics of North America* 23, no. 4 (November 2005): 959–975.

de Azambuja, Evandro, Philippe L Bedard, Thomas Suter, and Martine Piccart-Gebhart. "Cardiac Toxicity with anti-HER-2 Therapies: What Have We Learned so Far?" *Targeted Oncology* 4, no. 2 (April 2009): 77–88.

Barrett-Lee, P. J., J. M. Dixon, C. Farrell, A. Jones, R. Leonard, N. Murray, C. Palmieri, C. J. Plummer, A. Stanley, and M. W. Verrill. "Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk." *Ann Oncol* 20, no. 5 (May 1, 2009): 816–827.

Barry, Elly, Jorge A Alvarez, Rebecca E Scully, Tracie L Miller, and Steven E Lipshultz. "Anthracycline-induced Cardiotoxicity: Course, Pathophysiology, Prevention and Management." *Expert Opinion on Pharmacotherapy* 8, no. 8 (2007): 1039–1058.

Bates, M. "A Pharmacoeconomic Evaluation of the Use of Dexrazoxane in Preventing Anthracycline-Induced Cardiotoxicity in Patients with Stage IIIB or IV Metastatic Breast Cancer." *Clinical Therapeutics* 19, no. 1 (1997): 167–184.

Berg, W. A, J. D Blume, J. B Cormack, E. B Mendelson, D. Lehrer, M. Bohm-Velez, E. D Pisano, et al. "Combined Screening with Ultrasound and Mammography vs. Mammography Alone in Women at Elevated Risk of Breast Cancer." *Jama* 299, no. 18 (2008): 2151.

Berry, Colin, and John McMurray. "A Review of Quality-of-Life Evaluations in Patients with Congestive Heart Failure." *PharmacoEconomics* 16, no. 3 (1999): 247–271.

Berry, Donald A., Constance Cirrincione, I. Craig Henderson, Marc L. Citron, Daniel R. Budman, Lori J. Goldstein, Silvano Martino, et al. "Estrogen-receptor Status and Outcomes of Modern Chemotherapy for Patients with Node-positive Breast Cancer." *Journal of the American Medical Association* 295, no. 14 (2006): 1658.

Betti, Irene, Gabriele Castelli, Alessandro Barchielli, Cinzia Beligni, Vittorio Boscherini, Leonardo De Luca, Gianni Messeri, Mihai Gheorghiade, Alan Maisel, and Alfredo Zuppiroli. "The Role of N-terminal PRO-Brain Natriuretic Peptide and Echocardiography for Screening Asymptomatic Left Ventricular Dysfunction in a Population at High Risk for Heart Failure. The PROBE-HF Study." *Journal of Cardiac Failure* 15, no. 5 (June 2009): 377–384.

Biosite/Inverness Medical. "Biosite® Inc. Web Site -- Triage® BNP Test." *Biosite*, n.d. http://www.biosite.com/products/bnp.aspx.

Bird, Brian R. J. Healey, and Sandra M. Swain. "Cardiac Toxicity in Breast Cancer Survivors: Review of Potential Cardiac Problems." *Clinical Cancer Research* 14, no. 1 (January 1, 2008): 14 – 24.

Bock, Jay L. "Evaluation of Cardiac Injury and Function." In *Henry's Clinical Diagnosis and Management by Laboratory Methods.*, edited by Richard McPherson and Matthew R. Pincus, Chapter 18. Philadelphia: Saunders Elsevier, 2007.

Bootman, J.L., R.J. Townsend, and W.F. McGhan. *Principles of Pharmacoeconomics*. 3rd ed. Cincinnati OH: Harvey Whitney Books Co., 2005.

Braunwald, Eugene, Elliott M. Antman, John W. Beasley, Robert M. Califf, Melvin D. Cheitlin, Judith S. Hochman, Robert H. Jones, et al. "ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction: Executive Summary and Recommendations : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)." *Circulation* 102, no. 10 (September 5, 2000): 1193–1209.

Braunwald, Eugene. "Biomarkers in Heart Failure." *New England Journal of Medicine* 358, no. 20 (2008): 2148–2159.

Brennan, Alan, and Ron Akehurst. "Modeling in Health Economic Evaluation: What Is Its Place? What Is Its Value?" *Pharmacoeconomics* 17, no. 5 (2000): 445.

Bria, E., F. Cuppone, M. Fornier, C. Nisticò, P. Carlini, M. Milella, I. Sperduti, E. Terzoli, F. Cognetti, and D. Giannarelli. "Cardiotoxicity and Incidence of Brain Metastases After Adjuvant Trastuzumab for Early Breast Cancer: The Dark Side of the Moon? A Meta-analysis of the Randomized Trials." *Breast Cancer Research and Treatment* 109, no. 2 (2008): 231–239.

Briggs, Andrew H. "Handling Uncertainty in Cost-Effectiveness Models." *PharmacoEconomics* 17, no. 5 (May 2000): 479–500.

Briggs, Andrew, and Mark Sculpher. "An Introduction to Markov Modeling for Economic Evaluation" *PharmacoEconomics* 13, no. 4 (April 1998): 397–409.

Bristow, M. R., J. W. Mason, and J. R. Daniels. "Monitoring of Anthracycline Cardiotoxicity." *Cancer Treatment Reports* 62, no. 10 (October 1978): 1607–1608.

Bristow, Michael R., Arthur M. Feldman, Kirkwood F. Adams Jr., and Sidney Goldstein. "Selective Versus Nonselective B-blockade for Heart Failure Therapy: Are There Lessons to Be Learned from the COMET Trial?" *Journal of Cardiac Failure* 9, no. 6 (December 2003): 444–453.

Bristow, Michael R., Marcia B. Lopez, Jay W. Mason, Margaret E. Billingham, and Mark A. Winchester. "Efficacy and Cost of Cardiac Monitoring in Patients Receiving Doxorubicin." *Cancer* 50, no. 1 (1982): 32–41.

Brouwer, Werner B. F., Anthony J. Culyer, N. Job A. van Exel, and Frans F. H. Rutten. "Welfarism vs. Extra-welfarism." *Journal of Health Economics* 27, no. 2 (March 2008): 325–338.

Burstein, Harold J., and Eric P. Winer. "Primary Care for Survivors of Breast Cancer." *New* 343, no. 15 (October 12, 2000): 1086–1094.

Cardinale, D., M. T Sandri, A. Colombo, N. Colombo, M. Boeri, G. Lamantia, M. Civelli, et al. "Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-dose Chemotherapy." *Circulation* 109, no. 22 (2004): 2749.

Cardinale, D., M. T. Sandri, A. Martinoni, E. Borghini, M. Civelli, G. Lamantia, S. Cinieri, G. Martinelli, C. Fiorentini, and C. M. Cipolla. "Myocardial Injury Revealed by Plasma Troponin I in Breast Cancer Treated with High-dose Chemotherapy." *Annals of Oncology* 13, no. 5 (2002): 710.

Carson, Richard T. "Contingent Valuation: A User's Guide†." *Environmental Science & Technology* 34, no. 8 (April 1, 2000): 1413–1418.

Castellanos, Agustin, Alberto Interian Jr., and Robert J. Myerburg. "The Resting Electrocardiogram." In *Hurst's the Heart*, edited by Valentin Fuster, Chapter 13. New York: McGraw-Hill Medical, 2008.

Cheitlin, Melvin D., William F. Armstrong, Gerard P. Aurigemma, George A. Beller, Fredrick Z. Bierman, Jack L. Davis, Pamela S. Douglas, et al. "ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)." *Circulation* 108, no. 9 (September 2, 2003): 1146–1162.

Chien, Kenneth R. "Herceptin and the Heart -- A Molecular Modifier of Cardiac Failure." *N Engl J Med* 354, no. 8 (2006): 789–790.

Choi, J. C, J. D Chang, B. Seal, M. Tangirala, and C. D Mullins. "Risk and Cost of Anthracycline-induced Cardiotoxicity Among Breast Cancer Patients in the United States." *J Clin Oncol (Meeting Abstracts)* 27, no. 15S (2009): 1037–.

Christiansen, Stefan, and Rudiger Autschbach. "Doxorubicin in Experimental and Clinical Heart Failure." *European Journal of Cardio-Thoracic Surgery* 30, no. 4 (October 2006): 611–616.

Cianfrocca, M., and L. J Goldstein. "Prognostic and Predictive Factors in Early-stage Breast Cancer." *The Oncologist* 9, no. 6 (2004): 606.

Cil, T., A. M Kaplan, A. Altintas, A. M Akin, S. Alan, and A. Isikdogan. "Use of N-Terminal Pro-Brain Natriuretic Peptide to Assess Left Ventricular Function After Adjuvant Doxorubicin Therapy in Early Breast Cancer Patients: A Prospective Series." *Clinical Drug Investigation* 29, no. 2 (2009): 131–137.

Clarke, M, R Collins, S Darby, C Davies, P Elphinstone, E Evans, J Godwin, et al. "Effects of Radiotherapy and of Differences in the Extent of Surgery for Early Breast Cancer on Local Recurrence and 15-year Survival: An Overview of the Randomised Trials." *Lancet* 366, no. 9503 (December 17, 2005): 2087–2106.

Claxton, Karl. "Exploring Uncertainty in Cost-Effectiveness Analysis." *PharmacoEconomics* 26, no. 9 (June 2008): 781.

Cleland, John G.F., Jean-Claude Daubert, Erland Erdmann, Nick Freemantle, Daniel Gras, Lukas Kappenberger, Luigi Tavazzi, and the Cardiac Resynchronization -- Heart Failure (CARE-HF) Study Investigators. "The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure." *N Engl J Med* 352, no. 15 (April 14, 2005): 1539–1549.

Clerico, Aldo, Simona Vittorini, Claudio Passino, and Michele Emdin. "New and Emerging Biomarkers of Heart Failure." *Critical Reviews in Clinical Laboratory Sciences* 46, no. 3 (2009): 107–128.

Cohn, Jay, John G.F. Cleland, Jacobus Lubsen, Jeffrey S. Borer, Philippe Gabriel Steg, Michael Perelman, and Faiez Zannad. "Unconventional End Points in Cardiovascular Clinical Trials: Should We Be Moving Away From Morbidity and Mortality?" *Journal of Cardiac Failure* 15, no. 3 (April 2009): 199–205.

Colditz, G. A, W. C Willett, D. J Hunter, M. J Stampfer, J. A.E Manson, C. H Hennekens, B. A Rosner, and F. E Speizer. "Family History, Age, and Risk of Breast Cancer: Prospective Data from the Nurses' Health Study." *Jama* 270, no. 3 (1993): 338.

Collinson, P. "Analytical Performance of the N Terminal Pro B Type Natriuretic Peptide (NT-proBNP) Assay on the Elecsys^{TM} 1010 and 2010 Analysers." *European Journal of Heart Failure* 6, no. 3 (2004): 365–368.

Cowie, M. "Clinical Applications of B-type Natriuretic Peptide (BNP) Testing." *European Heart Journal* 24, no. 19 (2003): 1710–1718.

Cowie, M. R., P. Jourdain, A. Maisel, U. Dahlstrom, F. Follath, R. Isnard, A. Luchner, et al. "Clinical Applications of B-type Natriuretic Peptide (BNP) Testing." *European Heart Journal* 24, no. 19 (2003): 1710.

Curtis, Lesley H, Melissa A Greiner, Bradley G Hammill, Judith M Kramer, David J Whellan, Kevin A Schulman, and Adrian F Hernandez. "Early and Long-term Outcomes of Heart Failure in Elderly Persons, 2001-2005." *Arch Intern Med* 168, no. 22 (2008): 2481–2488.

Danias, Peter G., and Gary V. Heller. "Non-Invasive Methods for Measurement of Left Ventricular Systolic Dysfunction." In *Up To Date*. Waltham, MA.: Up To Date, 2010. www.uptodate.com.

Daugaard, G., U. Lassen, P. Bie, E. B Pedersen, K. T Jensen, U. Abildgaard, B. Hesse, and A. Kjaer. "Natriuretic Peptides in the Monitoring of Anthracycline Induced Reduction in Left Ventricular Ejection Fraction." *European Journal of Heart Failure* 7, no. 1 (2005): 87.

Dokainish, Hisham, William A. Zoghbi, Eunice Ambriz, Nasser M. Lakkis, Miguel A. Quinones, and Sherif F. Nagueh. "Comparative Cost-Effectiveness of B-Type Natriuretic Peptide and Echocardiography for Predicting Outcome in Patients With Congestive Heart Failure." *The American Journal of Cardiology* 97, no. 3 (February 1, 2006): 400–403.

Dolci, Alberto, Roberto Dominici, Daniela Cardinale, Maria T. Sandri, and Mauro Panteghini. "Biochemical Markers for Prediction of Chemotherapy-Induced Cardiotoxicity: Systematic Review of the Literature and Recommendations for Use." *American Journal of Clinical Pathology* 130, no. 5 (2008): 688–695.

Doust, Jenny A., Paul P. Glasziou, Eva Pietrzak, and Annette J. Dobson. "A Systematic Review of the Diagnostic Accuracy of Natriuretic Peptides for Heart Failure." *Arch Intern Med* 164, no. 18 (October 11, 2004): 1978–1984.

Doyle, John, Alfred Neugut, Judith Jacobson, Victor Grann, and Dawn Hershman. "Chemotherapy and Cardiotoxicity in Older Breast Cancer Patients: A Population-Based Study." *Journal of Clinical Oncology* 23, no. 34 (December 1, 2005): 8587–8605.

Dranitsaris, G., and T. M. Tran. "Economic Analyses of Toxicity Secondary to Anthracycline-based Breast Cancer Chemotherapy." *European Journal of Cancer* 31, no. 13–14 (1995): 2174–2180.

Drummond, Michael, and Alistair McGuire. *Economic Evaluation in Health Care : Merging Theory with Practice*. New York: Oxford University Press, 2001.

Drummond, Michael, Mark Sculpher, George Torrance, Bernie O'Brien, and Greg Stoddart. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, USA, 2005..

Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, et al. "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)." *European Journal of Cancer* 45, no. 2 (2009): 228–247.

Elmore, J. G, K. Armstrong, C. D Lehman, and S. W Fletcher. "Screening for Breast Cancer." *Jama* 293, no. 10 (2005): 1245.

Esserman, Laura J., and Bonnie N. Joe. "Diagnostic Evaluation of Women Suspected With Breast Cancer." *Up To Date*, September 2009. www.uptodate.com.

Ewald, B., D. Ewald, A. Thakkinstian, and J. Attia. "Meta-analysis of B Type Natriuretic Peptide and N-terminal Pro B Natriuretic Peptide in the Diagnosis of Clinical Heart Failure and Population Screening for Left Ventricular Systolic Dysfunction." *Internal Medicine Journal* 38, no. 2 (2008): 101–113.

Ewer, Michael S., and Robert S. Benjamin. "Formulae for Predicting the Likelihood of Developing Congestive Heart Failure Following Anthracycline Chemotherapy: Added Evidence for Early Cardiotoxicity." *Journal of Cardiac Failure* 11, no. 6, Supplement 1 (August 2005): S159.

Ewer, S. M, and M. S Ewer. "Cardiotoxicity Profile of Trastuzumab." *Drug Safety* 31, no. 6 (2008): 459–467.

Feola, Mauro, Ornella Garrone, Marcella Occelli, Antonella Francini, Alberto Biggi, Gianluca Visconti, Fabrizia Albrile, Marco Bobbio, and Marco Merlano. "Cardiotoxicity After Anthracycline Chemotherapy in Breast Carcinoma: Effects on Left Ventricular Ejection Fraction, Troponin I and Brain Natriuretic Peptide." *International Journal of Cardiology* (2009).

Ferrans, Victor J., and William C. Roberts. "Myocardial Biopsy: A Useful Diagnostic Procedure or Only a Research Tool?" *The American Journal of Cardiology* 41, no. 5 (May 1, 1978): 965–967.

Ferri, Fred F. "Laboratory Values and Interpretation of Results." In *Practial Guide to the Care of the Medical Patient*, Chapter 15. Philadelphia: Mosby/Elsevier, 2007. http://www.mdconsult.com.ezproxy.lib.utexas.edu/.

Flobbe, K., A. M Bosch, A. G.H Kessels, G. L Beets, P. J Nelemans, M. F von Meyenfeldt, and J. van Engelshoven. "The Additional Diagnostic Value of Ultrasonography in the Diagnosis of Breast Cancer." *Archives of Internal Medicine* 163, no. 10 (2003): 1194.

Flynn, Terry N. "Using Conjoint Analysis and Choice Experiments to Estimate QALY Values: Issues to Consider." *PharmacoEconomics* 28, no. 9 (2010): 711–722.

Francis, Gary S., Edmond H. Sonnenblick, W. H. Wilson Tang, and Philip Poole-Wilson. "Pathophysiology of Heart Failure." In *Hurst's the Heart*, Chapter 24. 12th ed. New York: McGraw-Hill Medical, 2008.

Frazier, Camille G., Karen P. Alexander, L. Kristin Newby, Susan Anderson, Erik Iverson, Milton Packer, Jay Cohn, Sidney Goldstein, and Pamela S. Douglas. "Associations of Gender and Etiology With Outcomes in Heart Failure With Systolic Dysfunction: A Pooled Analysis of 5 Randomized Control Trials." *Journal of the American College of Cardiology* 49, no. 13 (April 3, 2007): 1450–1458.

Froberg, Debra G., and Robert L. Kane. "Methodology for Measuring Health-state preferences--I: Measurement Strategies." *Journal of Clinical Epidemiology* 42, no. 4 (1989): 345–354.

Froberg, Debra G. and Robert L. Kane. "Methodology for Measuring Health-state preferences--II: Scaling Methods." *Journal of Clinical Epidemiology* 42, no. 5 (1989): 459–471.

Fryback, Dennis G., Erik J. Dasbach, Ronald Klein, Barbara E.K. Klein, Norma Dorn, Kathy Peterson, and Patrica A. Martin. "The Beaver Dam Health Outcomes Study." *Medical Decision Making* 13, no. 2 (June 1, 1993): 89 –102.

Galasko, Gavin I. W, Sophie C Barnes, Paul Collinson, Avijit Lahiri, and Roxy Senior. "What Is the Most Cost-effective Strategy to Screen for Left Ventricular Systolic Dysfunction: Natriuretic Peptides, the Electrocardiogram, Hand-held Echocardiography, Traditional Echocardiography, or Their Combination?" *European Heart Journal* 27, no. 2 (2006): 193–200.

Galderisi, M., F. Marra, R. Esposito, V. S Lomoriello, M. Pardo, and O. de Divitiis. "Cancer Therapy and Cardiotoxicity: The Need of Serial Doppler Echocardiography." *Cardiovascular Ultrasound* 5, no. 1 (2007): 4.

Gennari, A., B. Salvadori, S. Donati, C. Bengala, C. Orlandini, R. Danesi, M. Del Tacca, P. Bruzzi, and P. F Conte. "Cardiotoxicity of Epirubicin/paclitaxel-containing Regimens: Role of Cardiac Risk Factors." *Journal of Clinical Oncology* 17, no. 11 (1999): 3596.

Gianni, L., E. Munzone, G. Capri, F. Fulfaro, E. Tarenzi, F. Villani, C. Spreafico, A. Laffranchi, A. Caraceni, and C. Martini. "Paclitaxel by 3-hour Infusion in Combination with Bolus Doxorubicin in Women with Untreated Metastatic Breast Cancer: High Antitumor Efficacy and Cardiac Effects in a Dose-finding and Sequence-finding Study." *Journal of Clinical Oncology* 13, no. 11 (1995): 2688.

Glas, Afina S., Jeroen G. Lijmer, Martin H. Prins, Gouke J. Bonsel, and Patrick M. M. Bossuyt. "The Diagnostic Odds Ratio: a Single Indicator of Test Performance." *Journal of Clinical Epidemiology* 56, no. 11 (November 2003): 1129–1135.

Glickson, Jerry D, John R Forder, and John C Chatham. "Imaging of Cardiotoxicity." *Molecular Imaging: Official Journal of the Society for Molecular Imaging* 7, no. 3 (June 2008): 115–117.

Godolphin, William, John A. Holt, Lovell A. Jones, Duane E. Keith, Wendy J. Levin, Michael F. Press, Dennis J. Slamon, et al. "Studies of the HER-2-neu Proto-oncogene in Human Breast and Ovarian Cancer." *Science* 244 (1989): 707+.

Gold, Marthe R., Joanna E. Siegel, Louise B. Russell, and Milton C. Weinstein, eds. *Cost-effectiveness in Health and Medicine*. Oxford University Press US, 1996.

Goldberg, Lee R, and Mariell Jessup. "A Time to Be Born and a Time to Die." *Circulation* 116, no. 4 (2007): 360–362.

Gøtzsche, Peter C, and Margrethe Nielsen. "Screening for Breast Cancer with Mammography." Edited by The Cochrane Collaboration and Peter C Gøtzsche. *Cochrane Database of Systematic Reviews*, no. 10 (2011)

Grande, A M, M Rinaldi, S Sinelli, A M D'Armini, and M Viganŏ. "Heart Transplantation in Chemotherapeutic Dilated Cardiomyopathy." *Transplantation Proceedings* 35, no. 4 (June 2003): 1516–1518.

Green, S., and G. R Weiss. "Southwest Oncology Group Standard Response Criteria, Endpoint Definitions and Toxicity Criteria." *Investigational New Drugs* 10, no. 4 (1992): 239–253.

Grunfeld, Eva. "Optimizing Follow-up After Breast Cancer Treatment." *Current Opinion in Obstetrics and Gynecology* 21, no. 1 (2009): 92–96.

Gustafsson, Finn, Frank Steensgaard-Hansen, Jorn Badskjaer, Allan H. Poulsen, Pernille Corell, and Per Hildebrandt. "Diagnostic and Prognostic Performance of N-Terminal ProBNP in Primary Care Patients With Suspected Heart Failure." *Journal of Cardiac Failure* 11, no. 5, Supplement 1 (June 2005): S15–S20.

Guyatt, Gordon H., David H. Feeny, and Donald L. Patrick. "Measuring Health-Related Quality of Life." *Annals of Internal Medicine* 118, no. 8 (April 15, 1993): 622 –629.
Hall, C. "Essential Biochemistry and Physiology of (NT-pro)BNP." *European Journal of Heart Failure* 6, no. 3 (2004): 257–260.

Hall, Christian. "NT-ProBNP: The Mechanism Behind the Marker." *Journal of Cardiac Failure* 11, no. 5, Supplement 1 (June 2005): S81–S83.

Haq, Mohamed M., Sewa S. Legha, Janak Choksi, Gabriel N. Hortobagyi, Robert S. Benjamin, Michael Ewer, and Mohamed Ali. "Doxorubicin-induced Congestive Heart Failure in Adults." *Cancer* 56, no. 6 (1985): 1361–1365.

Harris, Lyndsay, Gerald Batist, Robert Belt, Douglas Rovira, Rudolph Navari, Nozar Azarnia, Lauri Welles, and Eric Winer. "Liposome-encapsulated Doxorubicin Compared with Conventional Doxorubicin in a Randomized Multicenter Trial as First-line Therapy of Metastatic Breast Carcinoma." *Cancer* 94, no. 1 (2002): 25–36.

Hartmann, L. C, T. A Sellers, M. H Frost, W. L Lingle, A. C Degnim, K. Ghosh, R. A Vierkant, et al. "Benign Breast Disease and the Risk of Breast Cancer." *New England Journal of Medicine* 353, no. 3 (2005): 229.

Hauptman, Paul J., Jason Swindle, Thomas E. Burroughs, and Mark A. Schnitzler. "Resource Utilization in Patients Hospitalized with Heart Failure: Insights from a Contemporary National Hospital Database." *American Heart Journal* 155, no. 6 (June 2008): 978–985.e1.

Hayes, Daniel F. "Follow-up of Patients with Early Breast Cancer." *N Engl J Med* 356, no. 24 (June 14, 2007): 2505–2513. Heart Failure Society of America. "HFSA 2010 Comprehensive Heart Failure Practice Guideline." *Journal of Cardiac Failure* 16, no. 6 (June 2010): e1–e194.

Heidenreich, Paul A, Matthew A Gubens, Gregg C Fonarow, Marvin A Konstam, Lynne W Stevenson, and Paul G Shekelle. "Cost-effectiveness of Screening with B-type Natriuretic Peptide to Identify Patients with Reduced Left Ventricular Ejection Fraction." *Journal of the American College of Cardiology* 43, no. 6 (2004): 1019–1026.

Hendel, Robert C., Daniel S. Berman, Marcelo F. Di Carli, Paul A. Heidenreich, Robert E. Henkin, Patricia A. Pellikka, Gerald M. Pohost, and Kim A. Williams. "ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine Endorsed by the American College of Emergency Physicians." *Journal Of The American College Of Cardiology* 53, no. 23 (June 9, 2009): 2201–2229.

Hershman, Dawn L, Russell B McBride, Andrew Eisenberger, Wei Yann Tsai, Victor R Grann, and Judith S Jacobson. "Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma." *J Clin Oncol* 26, no. 19 (2008): 3159–3165.

Hershman, Dawn L, and Theresa Shao. "Anthracycline Cardiotoxicity After Breast Cancer Treatment." *Oncology* 23, no. 3 (March 2009): 227–234.

Hinkle, A.S, S.C Truesdell, C.B Proukou, and L.S Constine. "Cardiotoxicity Related to Cancer Therapy." *Progress in Pediatric Cardiology* 8, no. 3 (January 1, 1998): 145–155.

Von Hoff, Daniel D, Maxwell W Layard, Peter Basa, Hugh L Davis, Ann L Von Hoff, Marcel Rozencweig, and Franco M. Muggia. "Risk Factors for Doxorubicin-lnduced Congestive Heart Failure." *Annals of Internal Medicine* 91, no. 5 (1979): 710–717.

Holmes, Ann M. "A Method to Elicit Utilities for Interpersonal Comparisons." *Medical Decision Making* 17, no. 1 (February 1, 1997): 10 –20.

Horacek, J M, R Pudil, L Jebavy, M Tichy, P Zak, and J Maly. "Assessment of Anthracycline-induced Cardiotoxicity with Biochemical Markers." *Experimental Oncology* 29, no. 4 (December 2007): 309–313.

Horner, M.J., L.A.G. Ries, M. Krapcho, N. Neyman, R. Aminou, N. Howlader, S.F. Altekruse, et al. "SEER Cancer Statistics Review 1975-2006." *Surveillance Epidemiology and End Results*, 2010. http://seer.cancer.gov/csr/1975_2006/index.html.

Howlader, N., A. M. Noone, M. Krapcho, N. Neyman, R. Aminou, W. Waldron, S.F. Altekruse, et al., eds. "SEER Cancer Statistics Review 1975-2008". Bethesda, Maryland: National Cancer Institute, 2011. http://seer.cancer.gov/csr/1975_2008/index.html.

Humphrey, L. L, M. Helfand, B. K.S Chan, and S. H Woolf. "Breast Cancer Screening: a Summary of the Evidence for the US Preventive Services Task Force." *Annals of Internal Medicine* 137, no. 5 Part 1 (2002): 347.

Hunt, Sharon Ann, William T. Abraham, Marshall H. Chin, Arthur M. Feldman, Gary S. Francis, Theodore G. Ganiats, Mariell Jessup, Marvin A. Konstam, Donna M. Mancini, and Keith Michl. "2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation." *Journal of the American College of Cardiology* 53, no. 15 (2009): e1–e90.

Hurria, Arti, and Clifford Hudis. "Follow-up Care of Breast Cancer Survivors." *Critical Reviews in Oncology/Hematology* 48, no. 1 (2003): 89–99.

Inadomi, J. M. "Decision Analysis and Economic Modelling: a Primer." *European Journal of Gastroenterology & Hepatology* 16, no. 6 (2004): 535.

Isner, Jeffrey M., Victor J. Ferrans, Steven R. Cohen, Bruce G. Witkind, Renu Virmani, John S. Gottdiener, J.Robert Beck, and William C. Roberts. "Clinical and Morphologic Cardiac Findings After Anthracycline Chemotherapy: Analysis of 64 Patients Studied at Necropsy." *The American Journal of Cardiology* 51, no. 7 (April 1983): 1167–1174.

Jessup, Mariell, and Susan Brozena. "Heart Failure." *The New England Journal of Medicine* 348, no. 20 (May 15, 2003): 2007–2018.

Jones, A L, M Barlow, P J Barrett-Lee, P A Canney, I M Gilmour, S D Robb, C J Plummer, A M Wardley, and M W Verrill. "Management of Cardiac Health in Trastuzumab-treated Patients with Breast Cancer: Updated United Kingdom National Cancer Research Institute Recommendations for Monitoring." *British Journal of Cancer* 100, no. 5 (2009): 684–692.

Jones, Robin L, Charles Swanton, and Michael S Ewer. "Anthracycline Cardiotoxicity." *Expert Opinion on Drug Safety* 5, no. 6 (2006): 791–809.

Jorgensen, K. J, and P. C Gotzsche. "Overdiagnosis in Publicly Organised Mammography Screening Programmes: Systematic Review of Incidence Trends." *British Medical Journal* 339, no. jul09 1 (2009): b2587.

Kaiserová, Helena, Tomáš Šimůnek, Martin Štěrba, Gertjan J. M. Hartog, Ladislava Schröterová, Olga Popelová, Vladimír Geršl, Eva Kvasničková, and Aalt Bast. "New Iron Chelators in Anthracycline-induced Cardiotoxicity." *Cardiovascular Toxicology* 7, no. 2 (2007): 145–150.

Kapoor, Avina [1], and Victor G Vogel. "Prognostic Factors for Breast Cancer and Their Use in the Clinical Setting." *Expert Review of Anticancer Therapy* 5 (April 2005): 269–281.

Kelsey, J. L, and G. S Berkowitz. "Breast Cancer Epidemiology." *Cancer Research* 48, no. 20 (1988): 5615.

Key, T. J, P. K Verkasalo, and E. Banks. "Epidemiology of Breast Cancer." *The Lancet Oncology* 2, no. 3 (2001): 133–140.

Khatcheressian, J. L., A. C. Wolff, T. J. Smith, E. Grunfeld, H. B. Muss, V. G. Vogel, F. Halberg, M. R. Somerfield, and N. E. Davidson. "American Society of Clinical Oncology 2006 Update of the Breast Cancer Follow-Up and Management Guidelines in the Adjuvant Setting." *Journal of Clinical Oncology* 24, no. 31 (November 2006): 5091–5097.

Khunti, K, I. Squire, K.R. Abrams, and A.J. Sutton. "Accuracy of a 12-lead Electrocardiogram in Screening Patients with Suspected Heart Failure for Open Access Echocardiography: a Systematic Review and Meta-analysis." *European Journal of Heart Failure* 6, no. 5 (2004): 571–576.

Klocke, Francis J., Michael G. Baird, Beverly H. Lorell, Timothy M. Bateman, Joseph V. Messer, Daniel S. Berman, Patrick T. O'Gara, et al. "ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging—Executive Summary." *Circulation* 108, no. 11 (2003): 1404 –1418.

Kösters, Jan Peter, and Peter C Gøtzsche. "Regular Self-examination or Clinical Examination for Early Detection of Breast Cancer." Edited by The Cochrane Collaboration and Jan Peter Kösters. *Cochrane Database of Systematic Reviews*, no. 2 (2003).

Kouloubinis, A., L. Kaklamanis, N. Ziras, S. Sofroniadou, K. Makaritsis, S. Adamopoulos, I. Revela, A. Athanasiou, D. Mavroudis, and V. Georgoulias. "ProANP and NT-proBNP Levels to Prospectively Assess Cardiac Function in Breast Cancer Patients Treated with Cardiotoxic Chemotherapy." *International Journal of Cardiology* 122, no. 3 (2007): 195–201.

Kremer, L C M, H J H van der Pal, M Offringa, E C van Dalen, and P A Voûte. "Frequency and Risk Factors of Subclinical Cardiotoxicity After Anthracycline Therapy in Children: a Systematic Review." *Annals of Oncology: Official Journal of the European Society for Medical Oncology / ESMO* 13, no. 6 (June 2002): 819–829.

Krum, Henry, and William T Abraham. "Heart Failure." *The Lancet* 373, no. 9667 (March 14, 2009): 941–955.

Kumar, Vinay, Abul K. Abbas, Nelson Fausto, and Jon C. Aster. "Carcinoma of the Breast." In *Kumar: Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Saunders Elsevier, 2009. http://www.mdconsult.com.ezproxy.lib.utexas.edu/

Latini, Roberto, Serge Masson, Inder S. Anand, Emil Missov, Marjorie Carlson, Tarcisio Vago, Laura Angelici, et al. "Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients With Stable Chronic Heart Failure." *Circulation* 116, no. 11 (September 11, 2007): 1242–1249.

Lee, Ho Sup, Chang Bae Son, Seong Hoon Shin, and Yang Soo Kim. "Clinical Correlation Between Brain Natriutetic Peptide and Anthracyclin-induced Cardiac Toxicity." *Cancer Research and Treatment* 40, no. 3 (2008): 121.

Lefrak, E A, J Pitha, S Rosenheim, and J A Gottlieb. "A Clinicopathologic Analysis of Adriamycin Cardiotoxicity." *Cancer* 32, no. 2 (1973): 302–314.

de Lemos, James A, Darren K McGuire, and Mark H Drazner. "B-type Natriuretic Peptide in Cardiovascular Disease." *The Lancet* 362, no. 9380 (July 26, 2003): 316–322. Lenihan, Daniel J. "Cardiotoxicity and Optimal Treatment." *Journal of Supportive Oncology* 6, no. 2 (February 2008): 77–79.

Levy, Daniel, Satish Kenchaiah, Martin G Larson, Emelia J Benjamin, Michelle J Kupka, Kalon K. L Ho, Joanne M Murabito, and Ramachandran S Vasan. "Long-Term Trends in the Incidence of and Survival with Heart Failure." *N Engl J Med* 347, no. 18 (2002): 1397–1402.

Levy, W.C., D. Mozaffarian, and D.T. Linker. "Seattle Heart Failure Model - an Individualized Prediction of Mortality." *The Journal of Heart and Lung Transplantation* 25, no. 2, Supplement 1 (February 2006): S55.

Levy, Wayne C, Dariush Mozaffarian, David T Linker, Santosh C Sutradhar, Stefan D Anker, Anne B Cropp, Inder Anand, et al. "The Seattle Heart Failure Model: Prediction of Survival in Heart Failure." *Circulation* 113, no. 11 (2006): 1424–1433.

Leyland-Jones, Brian. "Trastuzumab: Hopes and Realities." *The Lancet Oncology* 3, no. 3 (March 2002): 137–144.

Li, Christopher I., Kathleen E. Malone, and Janet R. Daling. "Differences in Breast Cancer Stage, Treatment, and Survival by Race and Ethnicity." *Arch Intern Med* 163, no. 1 (January 13, 2003): 49–56.

Liao, Lawrence, Kevin J. Anstrom, John S. Gottdiener, Paul A. Pappas, David J. Whellan, Dalane W. Kitzman, Gerard P. Aurigemma, Daniel B. Mark, Kevin A. Schulman, and James G. Jollis. "Long-term Costs and Resource Use in Elderly Participants with Congestive Heart Failure in the Cardiovascular Health Study." *American Heart Journal* 153, no. 2 (February 2007): 245–252.

Lipshultz, S E, S P Sanders, A M Goorin, J P Krischer, S E Sallan, and S D Colan. "Monitoring for Anthracycline Cardiotoxicity." *Pediatrics* 93, no. 3 (March 1994): 433–437.

Lipshultz, Steven E, and Steven D Colan. "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer." *J Clin Oncol* 22, no. 5 (2004): 769–773.

Lipshultz, Steven E, Stuart R Lipsitz, Stephen E Sallan, Valeriano C. Simbre, Seema L Shaikh, Suzanne M Mone, Richard D Gelber, and Steven D Colan. "Long-Term Enalapril Therapy for Left Ventricular Dysfunction in Doxorubicin-Treated Survivors of Childhood Cancer." *J Clin Oncol* 20, no. 23 (2002): 4517–4522.

Lipshultz, Steven E., Steven D. Colan, Richard D. Gelber, Antonio R. Perez-Atayde, Stephen E. Sallan, and Stephen P. Sanders. "Late Cardiac Effects of Doxorubicin Therapy for Acute Lymphoblastic Leukemia in Childhood." *New England Journal of Medicine* 324, no. 12 (March 21, 1991): 808–815.

Loehr, Laura R., Wayne D. Rosamond, Patricia P. Chang, Aaron R. Folsom, and Lloyd E. Chambless. "Heart Failure Incidence and Survival (from the Atherosclerosis Risk in Communities Study)." *The American Journal of Cardiology* 101, no. 7 (April 1, 2008): 1016–1022.

Lu, Ping. "Monitoring Cardiac Function in Patients Receiving Doxorubicin." *Seminars in Nuclear Medicine* 35, no. 3 (July 2005): 197–201.

Lubien, E. "Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction: Comparison With Doppler Velocity Recordings." *Circulation* 105, no. 5 (February 2002): 595–601.

Macabasco-O'Connell, Aurelia, and Pamela S. Miller. "Update on Heart Failure Management. Biomarkers for Heart Failure." Edited by Marla De Jong and Lynn Doering. *Progress in Cardiovascular Nursing* 21, no. 4 (October 2006): 215–218.

Mackowiak, J. "Cost of Heart Failure to the Healthcare System." *The American Journal of Managed Care* 4, no. 6 Suppl (June 1998): S338–342.

Maisel, A. "B-type Natriuretic Peptide in the Diagnosis and Management of Congestive Heart Failure." *Cardiology Clinics* 19, no. 4 (November 2001): 557–571.

Maisel, A. "B-type Natriuretic Peptide Levels: A Potential Novel 'white Count' for Congestive Heart Failure." *Journal of Cardiac Failure* 7, no. 2 (2001): 183–193.

Maisel, A. "B-Type Natriuretic Peptide Levels: Diagnostic and Prognostic in Congestive Heart Failure: What's Next?" *Circulation* 105, no. 20 (2002): 2328–2331.

Maisel, Alan S, Padma Krishnaswamy, Richard M Nowak, James McCord, Judd E Hollander, Philippe Duc, Torbjørn Omland, et al. "Rapid Measurement of B-type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure." *The New England Journal of Medicine* 347, no. 3 (July 18, 2002): 161–167.

Maisel, Alan S, James McCord, Richard M Nowak, Judd E Hollander, Alan H.B Wu, Philippe Duc, Torbjørn Omland, et al. "Bedside B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure with Reduced or Preserved Ejection Fraction: Results from the Breathing Not Properly Multinational Study." *Journal of the American College of Cardiology* 41, no. 11 (June 4, 2003): 2010–2017.

Maisel, Alan S., Jen Koon, Padma Krishnaswamy, Radmila Kazenegra, Paul Clopton, Nancy Gardetto, Robin Morrisey, Alex Garcia, Albert Chiu, and Anthony De Maria. "Utility of B-natriuretic Peptide as a Rapid, Point-of-care Test for Screening Patients Undergoing Echocardiography to Determine Left Ventricular Dysfunction." *American Heart Journal* 141, no. 3 (March 2001): 367–374.

Mant, J, J Doust, A Roalfe, P Barton, M R Cowie, P Glasziou, D Mant, et al. "Systematic Review and Individual Patient Data Meta-analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic Strategies in Primary Care." *Health Technology Assessment (Winchester, England)* 13, no. 32 (July 2009): 1–207, iii.

Massie, Barry M. "Heart Failure: Pathophysiology and Diagnosis." In *Goldman: Cecil Medicine*, Chapter 58. Philadelphia: Saunders Elsevier, 2011. http://www.mdconsult.com.ezproxy.lib.utexas.edu/

McCullough, P. A, T. Omland, A. S Maisel, and others. "B-type Natriuretic Peptides: a Diagnostic Breakthrough for Clinicians." *Reviews in Cardiovascular Medicine* 4, no. 2 (2003): 72–80.

McCullough, P. A. "B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis From Breathing Not Properly (BNP) Multinational Study." *Circulation* 106, no. 4 (2002): 416–422.

McDonagh, T A, S D Robb, D R Murdoch, J J Morton, I Ford, C E Morrison, H Tunstall-Pedoe, J J McMurray, and H J Dargie. "Biochemical Detection of Left-ventricular Systolic Dysfunction." *Lancet* 351, no. 9095 (January 3, 1998): 9–13.

McMurray, John J. V. "Systolic Heart Failure." *N Engl J Med* 362, no. 3 (2010): 228–238.

McPherson, K, C. M. Steel, and J. M. Dixon. "ABC of Breast Diseases: Breast Cancer---epidemiology, Risk Factors, and Genetics." *British Medical Journal* 321, no. 7261 (September 9, 2000): 624–628.

Mehra, Mandeep R., Jon Kobashigawa, Randall Starling, Stuart Russell, Patricia A. Uber, Jayan Parameshwar, Paul Mohacsi, Sharon Augustine, Keith Aaronson, and Mark Barr. "Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates--2006." *The Journal of Heart and Lung Transplantation* 25, no. 9 (2006): 1024–1042.

Mehta, Paresh A, and Martin R Cowie. "Epidemiology and Pathophysiology of Heart Failure." *Medicine* 34, no. 6 (June 1, 2006): 210–214.

Miller-Davis, Claiborne, Sue Marden, and Nancy Kline Leidy. "The New York Heart Association Classes and Functional Status: What Are We Really Measuring?" *Heart & Lung: The Journal of Acute and Critical Care* 35, no. 4 (2006): 217–224.

Minotti, G. "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity." *Pharmacological Reviews* 56, no. 2 (2004): 185–229.

Minow, Robert A., Robert S. Benjamin, Elisa T. Lee, and Jeffrey A. Gottlieb. "Adriamycin Cardiomyopathy-risk Factors." *Cancer* 39, no. 4 (1977): 1397–1402. Missov, Emil, and Johannes Mair. "A Novel Biochemical Approach to Congestive Heart Failure: Cardiac Troponin T." *American Heart Journal* 138, no. 1 (July 1999): 95–99.

Missov, Emile, Charles Calzolari, and Bernard Pau. "Circulating Cardiac Troponin I in Severe Congestive Heart Failure." *Circulation* 96, no. 9 (November 4, 1997): 2953–2958. Morandi, P, P A Ruffini, G M Benvenuto, R Raimondi, and V Fosser. "Cardiac Toxicity of High-dose Chemotherapy." *Bone Marrow Transplant* 35, no. 4 (November 15, 2004): 323–334.

Moreb, Jan S., and David J. Oblon. "Outcome of Clinical Congestive Heart Failure Induced by Anthracycline Chemotherapy." *Cancer* 70, no. 11 (1992): 2637–2641. Moriates, Christopher, and Alan Maisel. "The Utility of Biomarkers in Sorting Out the Complex Patient." *The American Journal of Medicine* 123, no. 5 (May 2010): 393–399.

Mueller, Christian, Kirsten Laule-Kilian, Christian Schindler, Theresia Klima, Barbara Frana, Daniel Rodriguez, André Scholer, Michael Christ, and André P Perruchoud. "Cost-effectiveness of B-type Natriuretic Peptide Testing in Patients with Acute Dyspnea." *Archives Of Internal Medicine* 166, no. 10 (May 22, 2006): 1081–1087.

Mueller, Christian, André Scholer, Kirsten Laule-Kilian, Benedict Martina, Christian Schindler, Peter Buser, Matthias Pfisterer, and André P Perruchoud. "Use of B-type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea." *The New England Journal of Medicine* 350, no. 7 (February 12, 2004): 647–654.

Nakamae, Hirohisa, Kei Tsumura, Mika Akahori, Yoshiki Terada, Takahisa Yamane, Takeo Hayashi, Ikuko Saito, et al. "QT Dispersion Correlates with Systolic Rather Than Diastolic Parameters in Patients Receiving Anthracycline Treatment." *Internal Medicine* 43, no. 5 (2004): 379–387.

Nakamura, Motoyuki, Fumitaka Tanaka, Kenyu Sato, Toshie Segawa, and Masahide Nagano. "B-Type Natriuretic Peptide Testing for Structural Heart Disease Screening: A General Population-Based Study." *Journal of Cardiac Failure* 11, no. 9 (December 2005): 705–712.

Narang, R., J. G. F Cleland, L. Erhardt, S. G Ball, A. J. S Coats, A. J Cowley, H. J Dargie, A. S Hall, J. R Hampton, and A. Poole-Wilson. "Mode of Death in Chronic Heart Failure." *European Heart Journal* 17, no. 9 (1996): 1390–1403.

NCCN Breast Cancer Panel Members. "Breast Cancer Practice Guidelines V2.2011." Professional Organization. *National Comprehensive Cancer Network*, March 25, 2011. www.nccn.org.

NCCN Breast Cancer Panel Members. "Breast Cancer Screening and Diagnosis V1.2011." Professional Organization. *The National Comprehensive Cancer Network*, November 19, 2010. www.nccn.org.

NCCN Breast Cancer Risk Reduction Panel Members. "Breast Cancer Risk Reduction V3.2011." Professional Organization. *National Comprehensive Cancer Network*, September 8, 2011. www.nccn.org.

Nelson, Heidi D, Kari Tyne, Arpana Naik, Christina Bougatsos, Benjamin K Chan, and Linda Humphrey. "Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force." *Annals of Internal Medicine* 151, no. 10 (November 17, 2009): 727–737.

Nicolini, Francesco, and Tiziano Gherli. "Alternatives to Transplantation in the Surgical Therapy for Heart Failure." *European Journal of Cardio-Thoracic Surgery* 35, no. 2 (February 2009): 214–228.

Nielsen, D, JB Jensen, P Dombernowsky, O Munck, J Fogh, I Brynjolf, H Havsteen, and M Hansen. "Epirubicin Cardiotoxicity: a Study of 135 Patients with Advanced Breast Cancer." *J Clin Oncol* 8, no. 11 (November 1, 1990): 1806–1810.

Nielsen, O. W, T. A McDonagh, S. D Robb, and H. J Dargie. "Retrospective Analysis of Thecost-effectiveness of Using Plasmabrain Natriuretic Peptide Inscreening for Left Ventricularsystolic Dysfunction in the General Population." *Journal of the American College of Cardiology* 41, no. 1 (2003): 113–120.

Nishimura, Rick A., Raymond J. Gibbons, James F. Glockner, and A. Jamil Tajik. "Non-Invasive Cardiac Imaging: Echocardiography, Nuclear Cardiology and MRI/CT Imaging." In *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill Medical, 2008.

Nousiainen, Tapio, Esko Vanninen, Esa Jantunen, Jukka Puustinen, Jouko Remes, Arto Rantala, and Juha Hartikainen. "Concomitant Impairment of Left Ventricular Systolic and Diastolic Function During Doxorubicin Therapy: A Prospective Radionuclide Ventriculographic and Echocardiographic Study." *Leukemia & Lymphoma* 43 (January 2002): 1807–1811.

Nutter, A.L., T. Tanawuttiwat, and M.A. Silver. "Evaluation of Six Prognostic Models in 80 Heart Failure Patients with a Fatal Heart Failure Admission." *The Journal of Heart and Lung Transplantation* 28, no. 2, Supplement 1 (February 2009): S140.

O'Brien, P. J. "Cardiac Troponin Is the Most Effective Translational Safety Biomarker for Myocardial Injury in Cardiotoxicity." *Toxicology* (2007).

O'Malley, Michael S., and Suzanne W. Fletcher. "Screening for Breast Cancer With Breast Self-examination." *JAMA: The Journal of the American Medical Association* 257, no. 16 (April 24, 1987): 2196 –2203.

Oken, Martin M. M.D., Richard H. M.D. Creech, Douglass C. M.D. Tormey, John M.D. Horton, Thomas E. M.D. Davis, Eleanor T. McFadden, and Paul P. M.D. Carbone. "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group." *Journal of Clinical Oncology December 1982* 5, no. 6 (1982): 649–656.

Olsen, J. A., and R. D. Smith. "Theory Versus Practice: a Review of 'willingness-to-pay' in Health and Health Care." *Health Economics* 10, no. 1 (2001): 39–52.
Palmeri, S., V. Leonardi, M. Tamburo De Bella, A. Morabito, M. Vaglica, V. Accurso, F. Ferraù, et al. "Doxorubicin-Docetaxel Sequential Schedule: Results of Front-Line Treatment in Advanced Breast Cancer." *Oncology* 63, no. 3 (2002): 205–212.

Parker, Robert B., Jo E. Rodgers, and Larissa H. Cavallari. "Chapter 16: Heart Failure." In *Pharmacotherapy: A Pathophysiologic Approach*, edited by Joseph T. Dipiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, and L. Michael Posey. 7th ed. McGraw-Hill Medical, 2008. http://www.accesspharmacy.com.ezproxy.lib.utexas.edu/.

Patel, J. K., and J. A. Kobashigawa. "Heart Transplantation." *Circulation* 124, no. 4 (July 2011): e132–e134.

Peacock, W F. "The B-type Natriuretic Peptide Assay: a Rapid Test for Heart Failure." *Cleveland Clinic Journal of Medicine* 69, no. 3 (March 2002): 243–251.

Peacock, W. Frank, Teresa De Marco, Gregg C Fonarow, Deborah Diercks, Janet Wynne, Fred S Apple, Alan H. B Wu, and the ADHERE Investigators. "Cardiac Troponin and Outcome in Acute Heart Failure." *N Engl J Med* 358, no. 20 (2008): 2117–2126.

Pinder, M. C., Z. Duan, J. S. Goodwin, G. N. Hortobagyi, and S. H. Giordano. "Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer." *Journal of Clinical Oncology* 25, no. 25 (2007): 3808–3815.

Poole-Wilson, Philip A, Karl Swedberg, John GF Cleland, Andrea Di Lenarda, Peter Hanrath, Michel Komajda, Jacobus Lubsen, et al. "Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised Controlled Trial." *The Lancet* 362, no. 9377 (July 5, 2003): 7–13.

Potluri, Srinivasa, Hector O Ventura, Mahesh Mulumudi, and Mandeep R Mehra. "Cardiac Troponin Levels in Heart Failure." *Cardiology in Review* 12, no. 1 (February 2004): 21–25.

Rajput, Farzan S., Hari Gnanasekeram, Shiyam Satwani, James D. Davenport, Edward J. Gracely, Radha Gopalan, and Jagat Narula. "Choosing Metoprolol or Carvedilol in Heart Failure (a pre-COMET Commentary)." *The American Journal of Cardiology* 92, no. 2 (July 15, 2003): 218–221.

Rampaul, R.S., S. E. Pinder, C. W. Elston, and I. O. Ellis. "Prognostic and Predictive Factors in Primary Breast Cancer and Their Role in Patient Management: The Nottingham Breast Team." *European Journal of Surgical Oncology* 27 (2001): 229–238.

Rascati, K. L. *Essentials of Pharmacoeconomics*. Philadelphia: Wolters Kluwer Health, 2009.

Rector, Thomas S. "A Conceptual Model of Quality of Life in Relation to Heart Failure." *Journal of Cardiac Failure* 11, no. 3 (April 2005): 173–176.

Rector, Thomas S., Inder S. Anand, and Jay N. Cohn. "Relationships Between Clinical Assessments and Patients' Perceptions of the Effects of Heart Failure on Their Quality of Life." *Journal of Cardiac Failure* 12, no. 2 (March 2006): 87–92.

Redfield, Margaret M, Richard J Rodeheffer, Steven J Jacobsen, Douglas W Mahoney, Kent R Bailey, and John C. Burnett. "Plasma Brain Natriuretic Peptide to Detect Preclinical Ventricular Systolic or Diastolic Dysfunction: A Community-Based Study." *Circulation* 109, no. 25 (2004): 3176–3181.

Redfield, Margaret M., Bernard J. Gersh, Kent R. Bailey, and Richard J. Rodeheffer. "Natural History of Incidentally Discovered, Asymptomatic Idiopathic Dilated Cardiomyopathy." *The American Journal of Cardiology* 74, no. 7 (October 1, 1994): 737–739.

Rennert, G., S. Bisland-Naggan, O. Barnett-Griness, N. Bar-Joseph, S. Zhang, H. S Rennert, and S. A Narod. "Clinical Outcomes of Breast Cancer in Carriers of BRCA1 and BRCA2 Mutations." *New England Journal of Medicine* 357, no. 2 (2007): 115.

Rhoden, W, P Hasleton, and N Brooks. "Anthracyclines and the Heart." *Heart* 70, no. 6 (1993): 499–502.

Rodeheffer, Richard J. "Measuring Plasma B-type Natriuretic Peptide in Heart Failure: Good to Go in 2004?" *Journal of the American College of Cardiology* 44, no. 4 (2004): 740–749.

Roig, Eulalia. "Usefulness of Neurohormonal Markers in the Diagnosis and Prognosis of Heart Failure." *Eur Heart J Suppl* 8, no. suppl_E (2006): E12–17.

Rojas, M.P., E. Telaro, I Moschetti, L. Coe, R. Fossati, A. Liberati, and M.D.T Rosselli. "Follow-Up Strategies for Women Treated for Early Breast Cancer." *The Cochrane Database of Systematic Reviews*, no. 4 (2009). http://www.mrw.interscience.wiley.com/cochrane/

Ross, Jeffrey S. "Multigene Classifiers, Prognostic Factors, and Predictors of Breast Cancer Clinical Outcome." *Advances in Anatomic Pathology* 16, no. 4 (2009): 204–215.

Ryberg, M., D. Nielsen, T. Skovsgaard, J. Hansen, B. V. Jensen, and P. Dombernowsky. "Epirubicin Cardiotoxicity: An Analysis of 469 Patients with Metastatic Breast Cancer." *Journal of Clinical Oncology* 16, no. 11 (1998): 3502.

Ryberg, Marianne, Dorte Nielsen, Giuliana Cortese, Gitte Nielsen, Torben Skovsgaard, and Per Kragh Andersen. "New Insight Into Epirubicin Cardiac Toxicity: Competing Risks Analysis of 1097 Breast Cancer Patients." *J. Natl. Cancer Inst.* 100, no. 15 (2008): 1058–1067.

Sanderson, John E, Skiva K.W Chan, Gabriel Yip, Leata Y.C Yeung, Kam W Chan, Kenneth Raymond, and Kam S Woo. "Beta-blockade in Heart Failure: A Comparison of Carvedilol with Metoprolol." *Journal of the American College of Cardiology* 34, no. 5 (November 1, 1999): 1522–1528.

Sandri, Maria T., Michela Salvatici, Daniela Cardinale, Laura Zorzino, Rita Passerini, Paola Lentati, Maria Leon, Maurizio Civelli, Giovanni Martinelli, and Carlo M. Cipolla. "N-Terminal Pro-B-Type Natriuretic Peptide After High-Dose Chemotherapy: A Marker Predictive of Cardiac Dysfunction?" *Clin Chem* 51, no. 8 (August 1, 2005): 1405–1410.

Sandri, Maria Teresa, Daniela Cardinale, Laura Zorzino, Rita Passerini, Paola Lentati, Alessandro Martinoni, Giovanni Martinelli, and Carlo Maria Cipolla. "Minor Increases in Plasma Troponin I Predict Decreased Left Ventricular Ejection Fraction After High-Dose Chemotherapy." *Clin Chem* 49, no. 2 (February 1, 2003): 248–252.

Sarko, John, and Charles V Pollack. "Cardiac Troponins." *The Journal of Emergency Medicine* 23, no. 1 (July 2002): 57–65.

Saslow, Debbie, Carla Boetes, Wylie Burkee, Steven Harms, Martin Leach, Constance Lehman, Elizabeth Morris, et al. "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography." *CA: A Cancer Journal for Clinicians* 57, no. 2 (April 2007): 75–89.

Schuchter, Lynn M., Martee L. Hensley, Neal J. Meropol, and Eric P. Winer. "2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology." *J Clin Oncol* 20, no. 12 (June 15, 2002): 2895–2903.

Schwartz, R. G, W. B McKenzie, J. Alexander, P. Sager, A. D'Souza, A. Manatunga, P. E Schwartz, et al. "Congestive Heart Failure and Left Ventricular Dysfunction Complicating Doxorubicin Therapy* 1:: Seven-year Experience Using Serial Radionuclide Angiocardiography." *The American Journal of Medicine* 82, no. 6 (1987): 1109–1118.

"SEER Web Site", n.d. http://seer.cancer.gov/.

Seidman, Andrew, Clifford Hudis, Mary Kathryn Pierri, Steven Shak, Virginia Paton, Mark Ashby, Maureen Murphy, Stanford J. Stewart, and Deborah Keefe. "Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience." *J Clin Oncol* 20, no. 5 (March 1, 2002): 1215–1221.

Shaddy, Robert E., Stephanie L. Olsen, Michael R. Bristow, David O. Taylor, Emily A. Bullock, Lloyd Y. Tani, and Dale G. Renlund. "Efficacy and Safety of Metoprolol in the Treatment of Doxorubicin-induced Cardiomyopathy in Pediatric Patients." *American Heart Journal* 129, no. 1 (January 1995): 197–199.

Shan, Kesavan, A. Michael Lincoff, and James B Young. "Anthracycline-Induced Cardiotoxicity." *Annals of Internal Medicine* 125, no. 1 (1996): 47–58.

Shapiro, C. L, T. Ervin, L. Welles, N. Azarnia, J. Keating, and Daniel F Hayes. "Phase II Trial of High-Dose Liposome-Encapsulated Doxorubicin With Granulocyte Colony-Stimulating Factor in Metastatic Breast Cancer." *J Clin Oncol* 17, no. 5 (1999): 1435–.

Shapiro, C. L., P. H. Hardenbergh, R. Gelman, D. Blanks, P. Hauptman, A. Recht, D. F. Hayes, J. Harris, and I. C. Henderson. "Cardiac Effects of Adjuvant Doxorubicin and Radiation Therapy in Breast Cancer Patients." *Journal of Clinical Oncology* 16, no. 11 (1998): 3493.

Shapiro, Charles L., and Abram Recht. "Side Effects of Adjuvant Treatment of Breast Cancer." *N Engl J Med* 344, no. 26 (June 28, 2001): 1997–2008.

Shureiqi, I, S B Cantor, S M Lippman, D E Brenner, M E Chernew, and A M Fendrick. "Clinical and Economic Impact of Multiple Gated Acquisition Scan Monitoring During Anthracycline Therapy." *British Journal of Cancer* 86, no. 2 (January 21, 2002): 226–232.

Siegel, Rebecca, Elizabeth Ward, Otis Brawley, and Ahmedin Jemal. "Cancer Statistics, 2011." *CA: A Cancer Journal for Clinicians* 61, no. 4 (July 2011): 212–236.

Silber, Jeffrey H, Avital Cnaan, Bernard J Clark, Stephen M Paridon, Alvin J Chin, Jack Rychik, Alexa N Hogarty, et al. "Enalapril to Prevent Cardiac Function Decline in Long-Term Survivors of Pediatric Cancer Exposed to Anthracyclines." *J Clin Oncol* 22, no. 5 (2004): 820–828.

Singal, P., T. Li, D. Kumar, I. Danelisen, and N. Iliskovic. "Adriamycin-induced Heart Failure: Mechanisms and Modulation." *Molecular and Cellular Biochemistry* 207, no. 1 (2000): 77–86.

Singal, Pawan K, and Natasha Iliskovic. "Doxorubicin-Induced Cardiomyopathy." *N

Engl J Med 339, no. 13 (1998): 900–905.

Singletary, S. E., and J. L. Connolly. "Breast Cancer Staging: Working With the Sixth Edition of the AJCC Cancer Staging Manual." *CA: A Cancer Journal for Clinicians* 56, no. 1 (January 2006): 37–47.
Singletary, S. Eva, Craig Allred, Pandora Ashley, Lawrence W. Bassett, Donald Berry, Kirby I. Bland, Patrick I. Borgen, et al. "Revision of the American Joint Committee on Cancer Staging System for Breast Cancer." *Journal of Clinical Oncology* 20, no. 17 (September 2002): 3628 –3636.

Slamon, D., W. Eiermann, N. Robert, T. Pienkowski, M. Martin, M. Pawlicki, A. Chan, et al. "Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC-T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC-TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in HER-2 Positive Early Breast Cancer Patients: BCIRG 006 Study." *Breast Cancer Research and Treatment* 94 (December 2005): S1–S301.

Slamon, Dennis J., Brian Leyland-Jones, Steven Shak, Hank Fuchs, Virginia Paton, Alex Bajamonde, Thomas Fleming, et al. "Use of Chemotherapy Plus a Monoclonal Antibody Against HER-2 for Metastatic Breast Cancer That Overexpresses HER-2." *N Engl J Med* 344, no. 11 (September 29, 2001): 783–792.

Smith, Richard D. "Construction of the Contingent Valuation Market in Health Care:a Critical Assessment." *Health Economics* 12, no. 8 (August 1, 2003): 609–628.

Smith, Robert A, Vilma Cokkinides, Durado Brooks, Debbie Saslow, Mona Shah, and Otis W Brawley. "Cancer Screening in the United States, 2011." *CA: A Cancer Journal for Clinicians* 61, no. 1 (January 1, 2011): 8–30.

Sonnenberg, F. A., and J. R. Beck. "Markov Models in Medical Decision Making: A Practical Guide." *Medical Decision Making* 13, no. 4 (1993): 322–338.

Speyer, James. "Cardiac Dysfunction in the Trastuzumab Clinical Experience." *J Clin Oncol* 20, no. 5 (2002): 1156–1157.

Speyer, James L., Boris Kobrinsky, and Michael S. Ewer. "Cardiac Effects of Cancer Therapy." In *Abeloff: Abeloff's Clinical Oncology*, Chapter 63. Philadelphia: Churchill Livingstone/Elsevier, 2008.
http://www.mdconsult.com.ezproxy.lib.utexas.edu/das/book/body/192728276-2/0/1709/68.html?tocnode=55016586&fromURL=68.html#4-u1.0-B978-0-443-06694-8..50067-1_2072.

Strevel, Elizabeth L., and Lillian L. Siu. "Cardiovascular Toxicity of Molecularly

Targeted Agents." *European Journal of Cancer* 45, no. Supplement 1 (2009): 318–331.
Sun, Xin, and Thomas Faunce. "Decision-analytical Modelling in Health-care Economic Evaluations." *The European Journal of Health Economics* 9, no. 4 (2007): 313–323.

Suter, T. M., N. Cook-Bruns, and C. Barton. "Cardiotoxicity Associated with Trastuzumab (Herceptin) Therapy in the Treatment of Metastatic Breast Cancer." *The Breast* 13, no. 3 (2004): 173–183.

Suter, Thomas M., Marion Procter, Dirk J. van Veldhuisen, Michael Muscholl, Jonas Bergh, Chiara Carlomagno, Timothy Perren, et al. "Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial." *J Clin Oncol* 25, no. 25 (2007): 3859–3865.

Suzuki, T, K Yamaoki, O Nakajima, T Yamazaki, Y Yamada, H Akioka, Y Yazaki, and R Nagai. "Screening for Cardiac Dysfunction in Asymptomatic Patients by Measuring B-type Natriuretic Peptide Levels." *Japanese Heart Journal* 41, no. 2 (March 2000): 205–214.
Suzuki, T., D. Hayashi, T. Yamazaki, T. Mizuno, Y. Kanda, I. Komuro, M. Kurabayashi, et al. "Elevated B-type Natriuretic Peptide Levels After Anthracycline Administration* 1,* 2,* 3,* 4." *American Heart Journal* 136, no. 2 (1998): 362–363.

Swain, Sandra M., Fredrick S. Whaley, and Michael S. Ewer. "Congestive Heart Failure in Patients Treated with Doxorubicin." *Cancer* 97, no. 11 (2003): 2869–2879.

Takemura, G., and H. Fujiwara. "Doxorubicin-induced Cardiomyopathy from the Cardiotoxic Mechanisms to Management." *Progress in Cardiovascular Diseases* 49, no. 5 (2007): 330–352.

Tallaj, Jose A., Veronica Franco, Barry K. Rayburn, Laura Pinderski, Raymond L. Benza, Salpy Pamboukian, Brian Foley, and Robert C. Bourge. "Response of Doxorubicin-induced Cardiomyopathy to the Current Management Strategy of Heart Failure." *The Journal of Heart and Lung Transplantation* 24, no. 12 (December 2005): 2196–2201.

Tan-Chiu, E. "Assessment of Cardiac Dysfunction in a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel, With or Without Trastuzumab As Adjuvant Therapy in Node-Positive, Human Epidermal Growth Factor Receptor 2-Overexpressing Breast Cancer: NSABP B-31." *Journal of Clinical Oncology* 23, no. 31 (2005): 7811–7819.

Tang, W.H. Wilson, Gary S. Francis, David A. Morrow, L. Kristin Newby, Christopher P. Cannon, Robert L. Jesse, Alan B. Storrow, et al. "National Academy of Clinical

Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure." *Clinical Biochemistry* 41, no. 4–5 (March 2008): 210–221.

Therasse, P., S. G Arbuck, E. A Eisenhauer, J. Wanders, R. S Kaplan, L. Rubinstein, J. Verweij, et al. "New Guidelines to Evaluate the Response to Treatment in Solid Tumors." *Breast Cancer* 12 (2005): 16–27.

Trotti, A., R. Byhardt, J. Stetz, C. Gwede, B. Corn, K. Fu, L. Gunderson, B. McCormick, and others. "Common Toxicity Criteria: Version 2.0. an Improved Reference for Grading the Acute Effects of Cancer Treatment: Impact on Radiotherapy." *International Journal of Radiation Oncology* Biology* Physics* 47, no. 1 (2000): 13–47.

Trotti, A., A. D. Colevas, A. Setser, Valerie Rusch, David Jaques, Volker Budach, Corey Langer, et al. "CTCAE V3.0: Development of a Comprehensive Grading System for the Adverse Effects of Cancer Treatment." *Seminars in Radiation Oncology* 13, no. 3 (July 2003): 176–181.

Troughton, Richard W., and A. Mark Richards. "B-Type Natriuretic Peptides and Echocardiographic Measures of Cardiac Structure and Function." *JACC: Cardiovascular Imaging* 2, no. 2 (February 2009): 216–225.

Vasan, Ramachandran S. "Biomarkers of Cardiovascular Disease: Molecular Basis and Practical Considerations." *Circulation* 113, no. 19 (May 16, 2006): 2335–2362.

Veronesi, Umberto, Giuseppe Viale, Nicole Rotmensz, and Aron Goldhirsch. "Rethinking TNM: Breast Cancer TNM Classification for Treatment Decision-making and Research." *The Breast* 15, no. 1 (2006): 3–8.

Vitarelli, Antonio, Susan Tiukinhoy, Silvia Di Luzio, Manuela Zampino, and Mihai Gheorghiade. "The Role of Echocardiography in the Diagnosis and Management of Heart Failure." *Heart Failure Reviews* 8, no. 2 (April 1, 2003): 181–189.

Vogel, C., M. A. Cobleigh, D. Tripathy, J. C. Gutheil, L. N. Harris, L. Fehrenbacher, D. J. Slamon, et al. "First-line, Single-agent Herceptin® (trastuzumab) in Metastatic Breast Cancer: a Preliminary Report." *European Journal of Cancer* 37, no. Supplement 1 (January 2001): 25–29.

van der Wal, Martje H.L., Tiny Jaarsma, Debra K. Moser, Nic J. G. M. Veeger, Wiek H. van Gilst, and Dirk J. van Veldhuisen. "Compliance in Heart Failure Patients: The Importance of Knowledge and Beliefs." *European Heart Journal* 27, no. 4 (February 2006): 434 –440.

van der Wal, Martje H.L., Tiny Jaarsma, and Dirk J. van Veldhuisen. "Non-compliance in Patients with Heart Failure; How Can We Manage It?" *European Journal of Heart Failure* 7, no. 1 (January 1, 2005): 5 –17.

Warner, Ellen, Hans Messersmith, Petrina Causer, Andrea Eisen, Rene Shumak, and Donald Plewes. "Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer." *Annals of Internal Medicine* 148, no. 9 (May 6, 2008): 671 –679.

Weaver, Sandra K., Phillip K. Fulkerson, Richard P. Lewis, and Carl V. Leier. "A Paucity of Chronic Electrocardiographic Changeswith Adriamycin Therapy." *Journal of Electrocardiology* 11, no. 3 (1978): 233–238.

Wieczorek, S. "A Rapid B-type Natriuretic Peptide Assay Accurately Diagnoses Left Ventricular Dysfunction and Heart Failure: A Multicenter Evaluation." *American Heart Journal* 144, no. 5 (November 2002): 834–839.

Woodward, Wendy A., Eric A. Strom, Susan L. Tucker, Marsha D. McNeese, George H. Perkins, Naomi R. Schechter, S. Eva Singletary, et al. "Changes in the 2003 American Joint Committee on Cancer Staging for Breast Cancer Dramatically Affect Stage-Specific Survival." *Journal of Clinical Oncology* 21, no. 17 (2003): 3244 –3248.

Wooster, Richard, and Barbara Weber. "Breast and Ovarian Cancer." *New England Journal of Medicine* 348, no. 23 (June 5, 2003): 2339–47.

Wouters, Karlijn A., Leontien C. M. Kremer, Tracie L. Miller, Eugene H. Herman, and Steven E. Lipshultz. "Protecting Against Anthracycline-induced Myocardial Damage: a Review of the Most Promising Strategies." *British Journal of Haematology* 131, no. 5 (2005): 561–578.

Wu, Audrey H. "Cardiotoxic Drugs: Clinical Monitoring and Decision Making." *Heart* 94, no. 11 (July 2008): 1503–1509.

Yaziji, Hadi, Lynn C. Goldstein, Todd S. Barry, Robert Werling, Harry Hwang, Georgiana K. Ellis, Julie R. Gralow, Robert B. Livingston, and Allen M. Gown. "HER-2 Testing in Breast Cancer Using Parallel Tissue-Based Methods." *JAMA: The Journal of the American Medical Association* 291, no. 16 (April 28, 2004): 1972 –1977.

Yeh, Edward T. H., and Courtney L. Bickford. "Cardiovascular Complications of Cancer Therapy: Incidence, Pathogenesis, Diagnosis, and Management." *Journal of the American College of Cardiology* 53, no. 24 (June 16, 2009): 2231–2247.

Yeh, Edward T. H., Ann T. Tong, Daniel J. Lenihan, S. Wamique Yusuf, Joseph Swafford, Christopher Champion, Jean-Bernard Durand, Harry Gibbs, Alireza Atef Zafarmand, and Michael S. Ewer. "Cardiovascular Complications of Cancer Therapy." *Circulation* 109, no. 25 (June 29, 2004): 3122 –3131.

Zomer, Ella, Danny Liew, and Bert Boffa. "Cost-effectiveness of Screening BNP-levels in Patients At-risk of Asymptomatic Left Ventricular Dysfunction." *Heart, Lung and Circulation* 17, no. Supplement 1 (2008): S53.

Zubrod, Charles G., Marvin Schneiderman, Emil Frei III, Clyde Brindley, G. Lennard Gold, Bruce Shnider, Raul Oviedo, et al. "Appraisal of Methods for the Study of Chemotherapy of Cancer in Man: Comparative Therapeutic Trial of Nitrogen Mustard and Triethylene Thiophosphoramide." *Journal of Chronic Diseases* 11, no. 1 (January 1960): 7–33.