

City University of New York (CUNY)

CUNY Academic Works

Dissertations and Theses

City College of New York

2016

Improving Medicare & Medicaid Reimbursement Framework for Molecular Diagnostics Tests Using Gene Sequencing: A Case Study in Health Economics

Advait Apte
CUNY City College

[How does access to this work benefit you? Let us know!](#)

More information about this work at: https://academicworks.cuny.edu/cc_etds_theses/662

Discover additional works at: <https://academicworks.cuny.edu>

This work is made publicly available by the City University of New York (CUNY).
Contact: AcademicWorks@cuny.edu

Improving Medicare & Medicaid Reimbursement Framework for Molecular Diagnostics Tests Using Gene Sequencing: A Case Study in Health Economics

-Dr. Advait Apte¹, Dr. Prabal De^{1,2}, and Dr. Kevin Foster^{1,3}

¹Department of Economics, City College of New York, New York, NY 10031

²Thesis Advisor

³Second Reader

Abstract

Breast cancer is the second leading cause of deaths among women, as about one in eight women in the US will develop invasive breast cancer during their lifetime. After the diagnosis of breast cancer, chemotherapy is the commonly prescribed first line of treatment. In the recent past, research has shown that molecular diagnostic tests have revealed that about 20% of the tumors carry the HER-2 mutation on cell surface, which can be treated with the drug Herceptin, or *trastuzumab*, improving cancer free survival rates from 71.9% to 84.2% in five years.

However, in spite of the observed increase in survival rates, the question of economic value produced by adding Herceptin to the chemotherapy remains an open question. We developed a model to analyze the economic benefits of using molecular diagnostics to reveal actionable clinical alterations. We used cancer registry incidence data from the Surveillance, Epidemiology, and End Results (SEER) program to compare the incidence rates and survival years per patient in a broad population. The results were incorporated into an economic model to predict benefits derived, in terms of cost savings, by the breast cancer patients. Specifically, we

projected per patient life years saved by adding Herceptin to the chemotherapy. Using conservative estimates for the dollar value of each life year saved, which stands at \$100,000 in 2016 dollars, total savings from adding Herceptin to chemotherapy were \$36,925 per patient. Even stretching the cost estimates does not change the general results. This model, which can objectively compare two therapy regimes in terms of economic benefits derived by stakeholders, can be applied to evaluate the economic value of competing treatment regimes.

1. Introduction

According to National Cancer Institute (NCI) an estimated 1.7 million new cases of cancer will be diagnosed in the United States in 2016 and 600,000 people will die from the disease. In 2010 alone, US expenditures for cancer care totaled nearly \$125 billion and are estimated to reach \$156 billion in 2020¹. According to the same institute, compared to different types of common cancers, breast cancer is estimated to have the highest number of incidences and deaths in 2016, 246660 and 40450 respectively¹. The most common cause of hereditary breast cancer is an inherited mutation in the *BRCA1* and *BRCA2* genes^{2,3}. These genes encode for proteins, which restrict abnormal cell growth in normal cells. A version of these genes carrying mutations prevents them from doing their normal housekeeping functions which leads to development of cancer. When breast cancer patients were analyzed, genomic testing on breast cancer tumors revealed other important genes directly involved in cancer development. One of the more prominent ones is *ERBB2* gene. Recent studies, particularly concentrated on the *HER2* or *ERBB2* gene which makes HER2 proteins⁴⁻⁷, have revealed the critical role this protein plays in tumor growth. HER2 proteins function as receptors on the breast cells. In a normal functioning cell,

HER2 receptors control the breast cell growth, division, and self-repairs. But it has been shown that in about 25-30% of breast cancers, the *HER2* gene malfunctions by making multiple copies of it, an event known as *HER2* gene amplification. All these extra *HER2* genes lead to overexpression of HER2 protein causing breast cells to grow and divide in an uncontrolled manner. Breast cancers with *HER2* gene amplification or HER2 protein overexpression are termed as HER2-positive in the pathology report. HER2-positive breast cancers tend to grow faster and are more likely to spread and come back compared to HER2-negative breast cancers^{4,8-10}. In recent years, biopsies have confirmed that approximately 30% of breast cancer patients have been identified to carry this mutation, making it one of the most sought after drug target^{5,11}. Currently there are four different molecular diagnostic methods to ascertain the presence of HER2 mutation. 1) IHC test (ImmunoHistoChemistry)¹²: The IHC test determines if there is excessive HER2 protein in the cancer cells. The results are interpreted as follows: 0 (negative), 1+ (also negative), 2+ (borderline), or 3+ (positive — HER2 protein overexpression). 2) FISH test (Fluorescence In Situ Hybridization)¹³: The FISH test determines if there are extra copies of the *HER2* gene in the cancer cells. The results are interpreted as positive (*HER2* gene amplification) or negative (no *HER2* gene amplification). 3) SPoT-Light HER2 CISH test (Subtraction Probe Technology Chromogenic In Situ Hybridization)¹⁴: The SPoT-Light test determines if there are extra copies of the *HER2* gene in the cancer cells. The results are interpreted as positive (*HER2* gene amplification) or negative (no *HER2* gene amplification), and 4) Inform HER2 Dual ISH test (Inform Dual In Situ Hybridization)¹⁵: The Inform HER2 Dual ISH test determines if there are extra copies of the *HER2* gene in the cancer cells. The results are interpreted as positive (*HER2* gene amplification) or negative (no *HER2* gene amplification). Though There is no agreement on the best method for determining HER2 status, out of the four

testing methods mentioned above, FISH and IHC are the most widely used for clinical diagnosis and recommended by all current national testing guidelines. While IHC tests for detect HER2 receptor overexpression, FISH measures the level of HER2 gene amplification. Results observed with IHC assays vary a lot and there are several factors that may contribute to the variations including sensitivity and specificity of the antibodies, use of antigen retrieval techniques, antibody dilution, pH of buffer, and sensitivity and specificity of the detection system. On the other hand, FISH techniques has been shown to be a highly reproducible technique for HER2 testing, allowing prolonged storage of paraffin blocks that does not affect its sensitivity¹⁶.

Generally, only cancers that test positive in these tests respond to the drugs targeting HER2-positive breast cancers. Over the years, the primary line of therapy for targeting breast cancer has been chemotherapy^{17,18}. Several studies have shown that targeting the HER2 mutation by adding *Trastuzumab* or *Herceptin* to the chemotherapy drug cocktail have improved survival and relapse after initial treatment^{11,18-24}. In spite of its widespread use, no formal study has been conducted on the cost effectiveness of covering the molecular diagnostic tests that lead to the prescription of this drug in the United States. Participants in clinical studies the CMS relies on for coverage determinations differ substantially from the Medicare population. Most of the times sufficient data is not available on relevant subgroup populations in order to make coverage decisions²⁵. In many cases it has been observed that some of the scenarios that were deemed appropriate by medical service providers were conflicting with the clinical requirements of many payers, including the Medicare National Coverage Determination (NCD)²⁶. Some researchers have put the blame on federal advisory committees and the intra-committee dynamics for the discrepancy in coverage decision²⁷. Premarket evidence for drugs and molecular diagnostics has limited ability to assure reproducible long-term outcomes, efficacy in different practice settings, and

benefits and risks in underrepresented populations in trials which makes coverage determination challenging. These limitations particularly affect personalized medicine, where data is essential in determining the effects of a new drug or device in particular subgroups of patients based on preferences, genomics, and other relevant clinical factors²⁸. This uncertainty makes it important to evaluate of costs and benefits of prescribing Herceptin treatment based on molecular diagnostic results. Though several recent studies on evaluating the clinical utility²⁹ and costs³⁰⁻³² of using *Herceptin* with chemotherapy have been conducted, they do not include a cost effectiveness analysis by comparing treatment regimes across cross sectional patient data. A recent study performed on Canadian breast cancer patient data to measure cost effectiveness of *Herceptin* has used only three health states along with Canada specific EFS data which is not directly portable under US Medicare reimbursement framework³³. Few other studies to model economic costs of cancer exist but they too use a European payer framework for evaluation of costs making direct application to US cancer patient data difficult^{34,35}. Literature on modeling cancer costs is abundant with different methodologies such as discrete event simulation³⁶, Markov chain³⁷⁻³⁹, and web crawler approaches³⁸. The first two methods largely depend on accurately predicting the probabilities and rates of cancer incidence, treatments and population dynamics which can be a herculean task given changing patient characteristics and advancements in diagnostic technologies. Methodologies that depend upon extracting information from the Internet can produce inaccurate results due to lack of curated clinical data. Researchers have also developed many cancer specific models including thyroid⁴⁰, cervical⁴¹, lung^{35,42,43}, breast⁴⁴, and colorectal³⁵ cancers. But they all fall short in calculating per patient cost savings to be universally applicable. Hence we propose a novel method, which uses Medicare patient data from the Surveillance, Epidemiology, and End Results (SEER) database to model the

incremental cost savings by using mutation specific drug treatment in addition to chemotherapy⁴⁵. In the following study, we estimate per patient savings by comparing cancer free survival in two groups of patients harboring HER2 mutation, one that were treated with *Herceptin* along with chemotherapy versus those treated with chemotherapy alone. Though the model evaluates benefits of a breast cancer specific mutation-targeting drug, the methodology can be extended to evaluate other mutation specific treatments.

2. Methods

As shown in figure 1, we have developed a model to compare *Herceptin* usage in breast cancer patients. We start by estimating the number of patients who did and did not receive *Herceptin* treatment. In the next step we estimate the incremental survival and the incremental costs associated with *Herceptin* usage in this patient population. Finally we estimate the incremental economic value of the life-years saved for BC patients when treated with *Herceptin*.

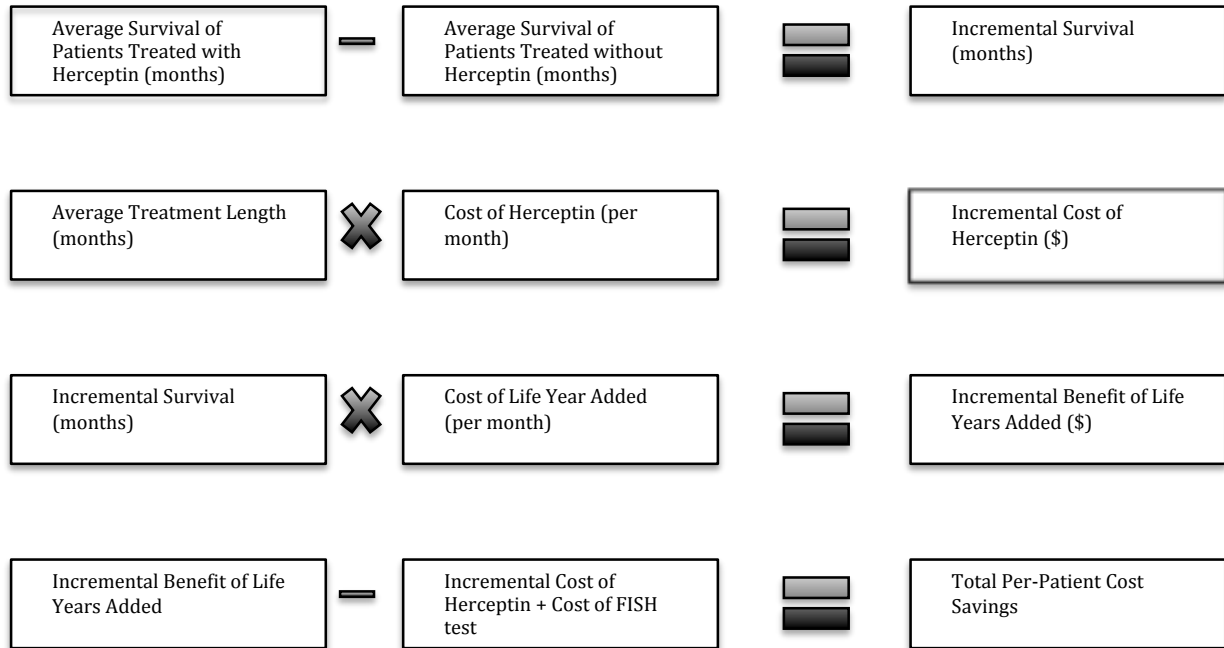


Fig 1. Flow of per-patient cost savings calculations.

2.1 Patient Selection

The National Cancer Institute collects incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas. The first recordings started in 1973 and the database consists every single reported cancer incidence from 9 cancer registries across the US⁴⁵. From the comprehensive SEER patient database, we selected only those breast cancer patients that harbor *Her2* gene mutation, otherwise referred as “HER2 positive” in the database (“DerHer2Recode”)*. In addition to the HER2 status, the dataset consists of HER2 summary result column, which was not a required data item for every breast cancer case diagnosed before 2010. As a result we were

* The SEER database also defines breast cancer subtypes (“BrstSubType”) by joining hormone receptor (HR which is a combination of estrogen receptor [ER] and progesterone receptor [PR]) and HER2 status⁴⁵. This variable is useful in determining HER2 status and facilitating the analysis of trends in breast cancer molecular subtypes. But due to high correlation between breast subtypes variable and derived HER2 recode variable (0.996), we decided to use only the HER2 recode variable, as it is easy to calculate and interpret.

only interested in cases having incidence date of 2010 or later as cases before 2010 have not reported the HER2 status of BC patients. For the 110,800 breast cancer cases diagnosed 2010 onwards, the number of patients with positive HER2 mutation was 12,255. We have considered the possibility that some patients will test HER2 positive even if they're actually HER2 negative and vice versa or in other words the possibility of Type I/II errors. Before applying the recoding algorithm for the cases with missing HER2 summary information, NCI has first applied it to cases for which directly coded HER2 summary information was available to assess agreement of the derived results to the coded results. Then the results obtained using these two approaches were compared, and more than 97% similarity was found⁴⁵. This leads us to believe that any Type I/II errors in the dataset are low enough not to affect the overall analysis.

Though *Herceptin* is generally used with patients harboring the HER2 mutation and breast cancer being in metastatic stage or has spread to other parts of the body, in 2006, it was approved by FDA as part of a treatment regime for the adjuvant treatment of HER2 positive breast cancer. Thus we have included both the patient populations, in situ and metastatic stage patients, in this study⁴⁶.

2.2 *Herceptin* Usage Determination

We divided the patient population into two groups, one treated with *Herceptin* and the other without. As we did not have access to the SEER-Medicare linked dataset and the SEER*Rx database, patient populations for both the groups were estimated using proxies for *Herceptin* usage based on the information provided in the SEER data. We have used the following method to estimate whether *Herceptin* was used as part of the therapy.

According to various sources, for uninsured patients, the cost of *Herceptin* can exceed \$70000 per year or \$5833 per month on the higher side while it can be as low as \$54,000 per year or \$4500 per month with some insurance providers⁴⁷⁻⁵⁰. We have used a conservative cost estimate of \$70000 per year or \$5833 per month for *Herceptin* treatment. Due to its high price, *Herceptin* is unaffordable to the uninsured patient population. Medicare part B covers 80% of the drug cost making it affordable to the population covered with some form of insurance^{51,52}. Hence, as a proxy for *Herceptin* usage, we have considered patients exhibiting HER2 mutation, having any type of insurance (Medicare, Medicaid, or private), and breast cancer incidence date 2010 and after. Similarly patients without any insurance coverage with identical HER2 status were grouped to create a population not treated with *Herceptin*.

2.3 Costs

Literature has shown that in clinical practice, treatment lengths of *Herceptin* vary due to large number of factors. Some oncologists, including scientists at Roche, maker of *Herceptin*, prescribe *Herceptin* for one full year. But in reality, most of the time, the treatment is effective only when used less than 3 months as the patients build resistance to the drug. Also patients may not survive the entire length of treatment as everyone responds differently to the drug. In addition, patients with HER2 mutation have relatively low survival rate as the mutation makes the tumor more aggressive. Due to these variations, it is unreasonable to assume that the average patient, who received *Herceptin*, received it for one full year. But, in absence of actual *Herceptin* usage data, we have used one year as the average length of *Herceptin* treatment. Generally, *Herceptin* comes in 400ml vials and is delivered in 40ml quantities with chemotherapy drug cocktail. Recently CMS has issued warnings concerning *Herceptin* billing. Hospitals and cancer

centers have consistently charged the CMS for whole 400 ml bottle regardless of actual usage and CMS policy dictates that the exact amount of *Herceptin* used for individual patient must be billed. Hence we believe that the marginal cost of whole *Herceptin* treatment, which though for a year, will overstate the actual cost of the drug to the CMS. Hence, for cost calculations, we have used a conservative estimate of \$5833 for one month's *Herceptin* supply allowing fractional drug usage wherever necessary.

Though it is difficult to put a dollar amount on the value of each life year for cancer patients, literature abounds with various cost of additional life year and in 2016 dollar, ranges from \$100,000 to \$165,000, according to some authors^{53,54}. This leads to a cost of \$8,333 to \$13,750 per month for individual cancer patient. Again, in this case, we have used the most conservative estimate of \$8,333 per month.

The last of the cost estimates we calculated is for the molecular diagnostic tests that determine existence of HER2 mutation in the BC tumor. Currently FISH test is the gold standard used for testing the presence of HER2 mutation and costs between \$537 and \$575 according to various providers^{55,56}. FISH test also has a well-established Medicare reimbursement framework in place. Hence going with the conservative estimate, we have used the cost of \$575 for the FISH test in our calculations

3. Data

The inputs for the model were derived from real world, heterogeneous, population-based data sources. HER2 status, survival, and insurance coverage were derived from the Surveillance, Epidemiology, and End Results (SEER) cancer registry data. The National Cancer Institute collects incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas. The first recordings started in 1973 and the database consists every single reported cancer incidence from 9 cancer registries across the US. According to the program website, the SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Data are available for cases diagnosed from 1973 and later for these registries with the exception of Seattle-Puget Sound and Atlanta. The Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively. The total number of cases documented in the SEER database is 9,176,963 with 8,234,845 cases being malignant. Cases are recorded for 9 different cancer types. The November 2015 submission of the breast dataset consists of information on 135 variables for 769,261 patients diagnosed between 1973 and 2013. Table 1 & 2 shows the summary statistics for the individual groups: treated and untreated.

Variable/ Statistic	Mean	SD	Median	IQR	Range
Age	58.14	13.80	57	48-67	18-100
Survival Month	21.25	13.77	21	9-33	0-47

Table 1. Age & survival statistics for patients with breast cancer incidence harboring HER2 mutation, diagnosed after 2009, and received Herceptin treatment from Medicare's cancer registry database.

Variable/ Statistic	Mean	SD	Median	IQR	Range
Age	49.1	9.13	50	42-57	25-64
Survival Month	18.76	13.34	17	8-28	0-47

Table 2. Age & survival statistics for patients with breast cancer incidence harboring HER2 mutation, diagnosed after 2009, and did not receive Herceptin treatment from Medicare’s cancer registry database.

Various other sources of data have been used for calculating the cost of treatment and cost of life years saved as described in the methods section. The primary determinant of life years saved is the number of months the patients have survived after initial treatment and comes directly from the SEER database. While figures for *Herceptin* costs come from well-established medical drug databases and insurance providers, cost of a life year is taken from previously published research, which have meticulously developed methodologies to accurately estimate the economic value of each additional year in cancer patients’ life.

Cost of molecular diagnostic tests is referred directly from vendor websites providing these services. In each case, the most conservative cost estimate is used for the analysis.

4. Results

As described in the methods section, using the ‘survival months’ data from the SEER database, we calculated the median survival for both the treated and untreated groups of patients. As seen

in table 1 and 2, the patient group treated with *Herceptin* had median survival of 21 months compared to 17 months for patients that did not receive *Herceptin* treatment.

We have considered several factors that might affect the survival of HER2+ BC patients. As shown in table 3, insurance status and age at diagnosis are significant predictors of survival while sex, race and marital status are weak predictors at best.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	22.68	0.82	27.57	< 0.001
Age at Diagnosis	-0.067	0.01	-7.29	< 0.001
Insurance status	0.81	0.23	3.55	< 0.001
Sex	0.04	1.57	0.03	< 1
Race	-0.015	0.01	-1.64	< 0.1
Marital status	-0.001	0.07	-0.01	< 0.1

Table 3. Results of linear model when survival months are regressed on various parameters.

Hence we can omit the confounding variables, which are not statistically significant to model a regression fit using only the Age at diagnosis and Insurance status. The model results, which are identical to the previous model, are shown in table 4.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	22.68	0.82	27.57	< 0.001
Age at Diagnosis	-0.067	0.01	-7.29	< 0.001
Insurance status	0.81	0.23	3.55	< 0.001

Table 4. Results of linear model when survival months are regressed on age and insurance status.

Going forward, we first created a dummy variable “Treat” which takes into account the insurance status and age at diagnosis indicating whether a particular patient received *Herceptin* treatment or not. A value of 0 indicates that the patient did not receive Herceptin treatment while a value of 1 indicates that Herceptin treatment was received. A linear model to estimate difference in the mean survival confirms that the treated group has an average incremental survival of 2.5 months, which is statistically significant at 5%. The results are shown in table 5.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	18.7565	0.9905	18.936	< 0.001
Treatment	2.4931	0.9986	2.497	< 0.05

Table 5. Results of linear model when survival months are regressed on binary treatment variable.

Next, we have assessed the robustness of the model using quantile regression fit to estimate the effects of outliers and calculate difference in the median survival months between treated and untreated groups. As indicated by the Treatment variable, the difference in median survival for the two groups is 4.43 months, which is statistically significant at 5%. Other confounding factors such as Race, Sex, and Marital status have minuscule effects on the median survival, which is not statistically significant. The results of quantile regression fit are presented in table 6.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	22.13	3.52	6.27	< 0.001
Treatment	4.43	1.41	3.12	< 0.05
Race	-0.02	0.01	-1.5	< 1
Sex	-0.54	1.55	-0.35	< 1
Marital Status	0.18	0.11	1.53	< 1

Table 6. Results of quantile regression for survival months vs. binary treatment variable along with other confounding variables.

Hence we have used a quantile regression model with Treatment as the only x variable. The results of this model are shown in table 7.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	17	1.27	13.38	< 0.001
Treatment	4	1.28	3.12	< 0.05

Table 7. Results of linear model when survival months are regressed on binary treatment variable.

Lastly, we have used propensity score model, which is used to improve parametric statistical models and reduce model dependence by preprocessing data with semi-parametric and non-parametric matching methods, to assess whether the difference in survival months between treated and untreated groups is stable. We have used the ‘*MatchIt*’ package for R developed by Stuart et. al^{57,58}. The matched dataset produced by their algorithm, using nearest matching method, is then used to regress survival months on the treatment variable. The results indicate that the difference in the mean survival of the two matched groups is statistically significant at 5%. The results are presented in table 8. When other confounding variables such as Race, Sex,

and Marital status are regressed against survival, sex of the patient seems to have a huge negative effect on the survival but the result is not statistically significant. Race and Marital status have a small effect on the overall survival but are not statistically significant. The only variable that has statistically significant effect on survival is the dummy treatment variable, which indicates whether the patient received Herceptin treatment, or not.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	32.65	27.47	1.19	< 1
Treatment	2.94	1.39	2.11	< 0.05
Race	-0.01	0.04	-0.34	< 1
Sex	-7.35	13.69	-0.53	< 1
Marital Status	0.36	0.38	0.95	< 1

Table 8. Results of linear regression for survival months of matched data vs. binary treatment variable along with other confounding variables.

Hence we have used only the treatment variable to predict survival as shown in table 9.

Coefficients:	Estimate	Std. Error	t value	Pr(> t)
Intercept	18.75	0.97	19.16	< 0.001
Treatment	3.07	1.38	2.22	< 0.05

Table 9. Results of linear regression for survival months of matched data vs. binary treatment variable.

This confirms that the difference in the survival for the treated and untreated groups is statistically significant and robust. We have considered using trimmed mean instead of average survival owing to the fact that *Herceptin* is not a maintenance drug. As median survival is a fully truncated mean and more stable than simple mean, we have used it as a survival estimator in the model. From the above models, the additional median months survived or the incremental survival rate for patients treated with *Herceptin* is 4 months compared to the untreated group. Using the methodology defined in earlier section, we calculated the incremental costs of *Herceptin* treatment by adding *Herceptin* cost for one year of treatment and one time cost of the FISH test, which equals \$70,575. The incremental benefit, which is the cost of incremental life years added, calculated using cost estimates mentioned in the methods section are \$33,332. This puts the incremental cost savings of *Herceptin* treatment at -\$37,243 per patient.

5. Conclusion

In this study we have used the SEER database to calculate the incremental per patient cost savings by using *Herceptin* along with standard chemotherapy drugs. Using the combination of insurance coverage and HER2 mutation status, as a proxy for *Herceptin* usage, we were able to calculate the per-patient cost savings, by using *Herceptin*, to be -\$37,243. These negative cost savings are the result of extending the overall survival of breast cancer patients with HER2 mutation by just four months with *Herceptin*. Substituting the relatively inexpensive FISH test for confirming positive HER2 mutation with more expensive test panels, which cost in the range of \$4500 without insurance, will not affect the overall outcome of this study. Based on medical

literature analyzing QALY assessment the threshold of cost effectiveness of medical interventions is thought to be \$50 000–\$100 000 in the US⁵⁹. Given the moderate side effects of *Herceptin* treatment, which primarily includes some minor cardiovascular complications compared to chemotherapy⁶⁰⁻⁶², we think a quality adjustment between the treated and untreated groups is not necessary. Hence, this study raises valid questions about the cost effectiveness of molecular diagnostic tests in identifying mutations in the breast cancer tumor that can be targeted with immunotherapy and extend the overall survival of BC patients. The generalized cost effectiveness model proposed in this study can be easily applied to evaluate the effectiveness of any molecular diagnostic test and its companion targeted therapy.

In the future, the accuracy of this study can be further enhanced by incorporating the pricing data from Medicare*Rx which records the actual price paid for *Herceptin* by the CMS and extracting details on the chemotherapy treatment information from the Medicare Linked Database. Gaining access to these databases requires a well-funded proposal from well-established institutions clearly showing its benefit to the CMS. Due to the limited scope of this modeling study, it does not fulfill the data access requirements in its present form. But the encouraging results obtained from this exercise can be used as a foundation for building sophisticated models in the future and to make a case for more advanced studies to be designed based on the Medicare*Rx database.

References

1. National Cancer Institute. Cancer statistics. <http://www.cancer.gov/about-cancer/understanding/statistics>. Updated 2016.
2. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *J Natl Cancer Inst*. 2003;95(19):1482-1485.
3. Van't Veer LJ, Dai H, Van De Vijver, Marc J, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415(6871):530-536.
4. Buza N, Roque DM, Santin AD. HER2/neu in endometrial cancer: A promising therapeutic target with diagnostic challenges. *Archives of Pathology and Laboratory Medicine*. 2014;138(3):343-350.
5. Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov*. 2013;3(2):224-237. doi: 10.1158/2159-8290.CD-12-0349 [doi].
6. Rafn B, Nielsen CF, Andersen SH, et al. ErbB2-driven breast cancer cell invasion depends on a complex signaling network activating myeloid zinc finger-1-dependent cathepsin B expression. *Mol Cell*. 2012;45(6):764-776.
7. Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: Pathophysiology, clinical use, and new advances in therapy. *Chemotherapy research and practice*. 2012;2012.
8. Kumar V, Abbas A, Aster J. Hemodynamic disorders, thromboembolism, and shock. *Robbins Basic Pathology, ninth ed., Philadelphia, ELSEVIER*. 2013:79-80.
9. Rüschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: A practical approach. *Modern Pathology*. 2012;25(5):637-650.

10. Santin AD, Bellone S, Roman JJ, McKenney JK, Pecorelli S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. *International Journal of Gynecology & Obstetrics*. 2008;102(2):128-131.
11. Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol*. 2013;31(16):1997-2003. doi: 10.1200/JCO.2012.45.6095 [doi].
12. Dabbs DJ. *Diagnostic immunohistochemistry*. Elsevier Health Sciences; 2013.
13. Tan V, Lu R, Tharayanil A, et al. P032 central lab HER2 testing by RT-PCR, IHC and FISH in locally HER2-neg, ER IBC with in situ carcinoma. *The Breast*. 2015(24):S37.
14. Perez EA, Cortés J, Gonzalez-Angulo AM, Bartlett JM. HER2 testing: Current status and future directions. *Cancer Treat Rev*. 2014;40(2):276-284.
15. Lim S, Cantillep A, Carpenter PM. Validation and workflow optimization of human epidermal growth factor receptor 2 testing using INFORM HER2 dual-color in situ hybridization. *Hum Pathol*. 2013;44(11):2590-2596.
16. Bilous M, Dowsett M, Hanna W, et al. Current perspectives on HER2 testing: A review of national testing guidelines. *Modern pathology*. 2003;16(2):173-182.
17. McArthur HL, Hudis CA. Breast cancer chemotherapy. *Cancer J*. 2007;13(3):141-147. doi: 10.1097/PPO.0b013e318074dc6f [doi].
18. Fumoleau P, Delgado FM, Delozier T, et al. Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol*. 1993;11(7):1245-1252.

19. Baselga J, Cortés J, Kim S, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119.
20. Lewis Phillips GD, Li G, Dugger DL, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res*. 2008;68(22):9280-9290. doi: 10.1158/0008-5472.CAN-08-1776 [doi].
21. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: Planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-3752. doi: 10.1200/JCO.2014.55.5730 [doi].
22. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. *N Engl J Med*. 2006;354(24):2619-2621.
23. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20(3):719-726.
24. Meza-Junco J, Au H, Sawyer MB. Critical appraisal of trastuzumab in treatment of advanced stomach cancer. *Cancer Manag Res*. 2011;3:57-64.
25. Dhruva SS, Redberg RF. Variations between clinical trial participants and medicare beneficiaries in evidence used for medicare national coverage decisions. *Arch Intern Med*. 2008;168(2):136-140.
26. Fogel RI, Epstein AE, Estes NM, et al. The disconnect between the guidelines, the appropriate use criteria, and reimbursement coverage decisions: The ultimate dilemma. *J Am Coll Cardiol*. 2014;63(1):12-14.

27. Lavertu S, Walters DE, Weimer DL. Scientific expertise and the balance of political interests: MEDCAC and medicare coverage decisions. *Journal of public administration research and theory*. 2012;22(1):55-81.
28. Daniel GW, Rubens EK, McClellan M. Coverage with evidence development for medicare beneficiaries: Challenges and next steps. *JAMA internal medicine*. 2013;173(14):1281-1282.
29. Davis CC, Zelnak A, Eley JW, Goldstein DA, Switchenko JM, McKibbin T. Clinical utility of routine cardiac monitoring in breast cancer patients receiving trastuzumab. *Ann Pharmacother*. 2016. doi: 1060028016654160 [pii].
30. Cloutier M, Guerin A, Heroux J, et al. Abstract P4-14-03: What are the real-world treatment patterns and medical costs in patients with metastatic breast cancer treated with ado-trastuzumab emtansine? *Cancer Res*. 2016;76(4 Supplement):P4-14-03-P4-14-03.
31. Romero PM, Gil RM. Trastuzumab emtansine in locally advanced or metastatic HER2 positive breast cancer; GENESIS-SEFH drug evaluation reporta. *Artículo especial*. 2015;39(3):171-175.
32. Ponzetti C, Canciani M, Farina M, Era S, Walzer S. Potential resource and cost saving analysis of subcutaneous versus intravenous administration for rituximab in non-hodgkin's lymphoma and for trastuzumab in breast cancer in 17 italian hospitals based on a systematic survey. *ClinicoEconomics and Outcomes Research: CEOR*. 2016;8:227.
33. Attard C, Pepper A, Brown S, et al. Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in canada. *Journal of medical economics*. 2015;18(3):173-188.
34. Olesen J, Gustavsson A, Svensson M, Wittchen H, Jönsson B. The economic cost of brain disorders in europe. *European Journal of Neurology*. 2012;19(1):155-162.

35. Hoyle M, Crathorne L, Peters J, et al. The clinical effectiveness and cost-effectiveness of cetuximab (mono-or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal no. 150 and part review of technology appraisal no. 118): A systematic review and economic model. . 2013.
36. Close A, Robertson C, Rushton S, et al. Comparative cost-effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of men with localised prostate cancer: A health technology assessment from the perspective of the UK national health service. *Eur Urol*. 2013;64(3):361-369.
37. Li H, Robinson KA, Anton B, Saldanha IJ, Ladenson PW. Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. *J Clin Endocrinol Metab*. 2011;96(11):E1719-26. doi: 10.1210/jc.2011-0459 [doi].
38. Beynon R, Hawkins J, Laing R, et al. The diagnostic utility and cost-effectiveness of selective nerve root blocks in patients considered for lumbar decompression surgery: A systematic review and economic model. *Health Technol Assess*. 2013;17(19):1-88, v-vi. doi: 10.3310/hta17190 [doi].
39. Benedict A, Figlin RA, Sandstrom P, et al. Economic evaluation of new targeted therapies for the first-line treatment of patients with metastatic renal cell carcinoma. *BJU Int*. 2011;108(5):665-672. doi: 10.1111/j.1464-410X.2010.09957.x [doi].
40. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. *Cancer Epidemiol Biomarkers Prev*. 2013;22(7):1252-1259. doi: 10.1158/1055-9965.EPI-13-0242 [doi].

41. Della Palma P, Moresco L, Giorgi Rossi P. Health technology assessment report: Computer-assisted pap test for cervical cancer screening. *Epidemiol Prev.* 2012;36(5 Suppl 3):e1-43.
42. Brown T, Pilkington G, Bagust A, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: A systematic review and economic evaluation. *Health Technol Assess.* 2013;17(31):1-278. doi: 10.3310/hta17310 [doi].
43. Rintoul RC, Glover MJ, Jackson C, et al. Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: A health economics analysis of the ASTER trial from a european perspective. *Thorax.* 2014;69(7):679-681. doi: 10.1136/thoraxjnl-2013-204374 [doi].
44. Rouzier R, Pronzato P, Chéreau E, Carlson J, Hunt B, Valentine WJ. Multigene assays and molecular markers in breast cancer: Systematic review of health economic analyses. *Breast Cancer Res Treat.* 2013;139(3):621-637.
45. Surveillance, epidemiology, and end results (SEER) program (www.seer.cancer.gov) research data (1973-2013), national cancer institute, DCCPS, surveillance research program, surveillance systems branch, released april 2016, based on the november 2015 submission. . 2016.
46. Genentech I. **FDA approves herceptin for the adjuvant treatment of HER2-positive node-positive breast cancer.** . 2006.
47. Barrett A, Roques T, Small M, Smith RD. How much will herceptin really cost? *BMJ : British Medical Journal.* 2006;333(7578):1118-1120. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1661755/>. doi: 10.1136/bmj.39008.624051.BE.
48. <http://www.truemedcost.com/herceptin-price/>. **Herceptin price.** .

49. Nordqvist C. **One year on herceptin for breast cancer ideal.** . 2012.
50. Fairs S. Living and dying might depend on cost. . 2015.
51. Medicare.gov. **What part B covers. What Part B covers** Web site. <https://www.medicare.gov/what-medicare-covers/part-b/what-medicare-part-b-covers.html>.
52. Centers for Medicare and Medicaid Services. **Welcome to the medicare coverage database.** . 2016.
53. Yabroff KR, Bradley CJ, Mariotto AB, Brown ML, Feuer EJ. Estimates and projections of value of life lost from cancer deaths in the united states. *J Natl Cancer Inst.* 2008;100(24):1755-1762. doi: 10.1093/jnci/djn383 [doi].
54. Durkee BY, Qian Y, Pollom EL, et al. Cost-effectiveness of pertuzumab in human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol.* 2016;34(9):902-909. doi: 10.1200/JCO.2015.62.9105 [doi].
55. Greenwood Genetic Center. **FISH for congenital anomalies. FISH for Congenital Anomalies** Web site. <http://www.ggc.org/diagnostic/tests-costs/test-finder/fish-for-congenital-anomalies.html>.
56. Science Exchange. Fish. FISH Web site. <https://www.scienceexchange.com/services/fish>.
57. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political analysis.* 2007;15(3):199-236.
58. King G, Imai K, Stuart EA. MatchIt: Nonparametric preprocessing for parametric causal inference. . 2007.

59. Shiroywa T, Sung Y, Fukuda T, Lang H, Bae S, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: What is the threshold of cost effectiveness? *Health Econ.* 2010;19(4):422-437.
60. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nature reviews Drug discovery.* 2010;9(4):325-338.
61. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: A position statement from the heart failure association of the european society of cardiology. *European journal of heart failure.* 2011;13(1):1-10.
62. Minami M, Matsumoto S, Horiuchi H. Cardiovascular side-effects of modern cancer therapy. *Circulation Journal.* 2010;74(9):1779-1786.