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

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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 2020[1]. 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 respectively[1]. 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 proteins[4-7], 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 sensitivity[16]. 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 decisions[25]. 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 decision[27]. 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 factors[28]. 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 utility[29]and costs [30-32] 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 framework[33]. 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 caner costs is abound with different methodologies such as discrete event simulation[36], Markov chain[37-39], and web crawler approaches[38]. 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 thyroid[40], cervical[41], lung[35,42,43], breast[44], and colorectal[35] 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 chemotherapy[45]. 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*.

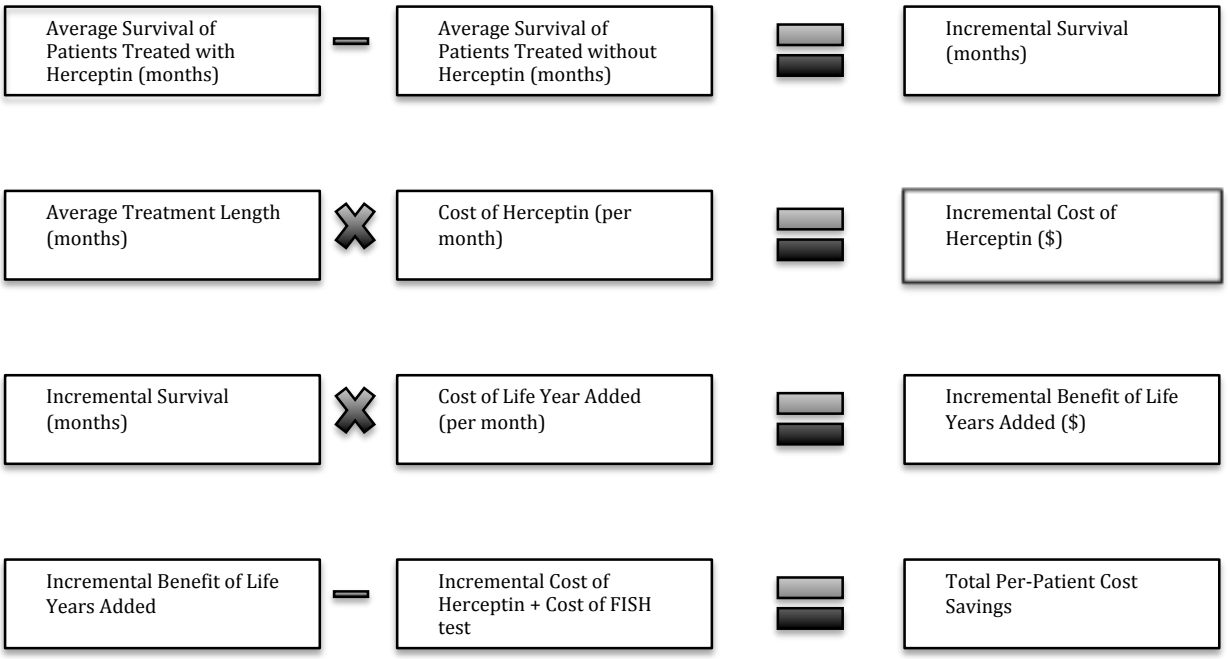

Fig 1. Flow of per-patient cost savings calculations.

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 US[45]. 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 status[45]. 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 found[45]. 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 study[46].

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 providers[47-50]. 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 US[59]. Given the moderate side effects of *Herceptin* treatment, which primarily includes some minor cardiovascular complications compared to chemotherapy[60-62], 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.

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