ECONOMIC EVALUATION OF 21-GENE ASSAY FOR EARLY STAGE BREAST CANCER PATIENTS FROM THE PERSPECTIVE OF THE CHINESE HEALTH CARE SYSTEM

by

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STATEMENT OF THESIS APPROVAL

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ABSTRACT

Traditional prognostic tools tended to overestimate the risk of cancer recurrence and recommend adjuvant chemotherapy plus tamoxifen for most of early stage breast cancer (ESBC) patients. 21-gene assay is validated as a better predictor that may support this decision-making process. Although the cost-effectiveness of 21-gene assay in developed countries is well researched, because of with huge differences in epidemiology, treatment, and healthcare system, these results cannot be generalized to China easily. This study aimed to evaluate the potential economic impact of incorporating 21-gene assay on Chinese ESBC patients.

A cost-effectiveness analysis with a decision tree and Markov model was performed based on the validation studies of 21-gene assay and published literature. A hypothetical cohort of 10,000 Chinese female patients with LN-, ER+, HER2- ESBC at the age of 45 were chosen to undergo treatment guided by either 21-gene assay or NCCN guideline Chinese version. Costs were estimated under the Chinese health care system, from the health care provider's perspective, reported in 2008 Chinese Yuan (¥). Total costs, Quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) were estimated as outcome measures.

Under base case analysis with the AC regimen as adjuvant chemotherapy, 21-gene assay saves ¥11 125 (US$1 628) with a higher QALY of 0.30 year per patient over 10

years. Replacing the chemotherapy with TC regimen results in an even larger cost saving of ¥13 285 (US$ 1 934) but less effective gain of 0.24 year. Although overall results were sensitive to the cost of 21-gene assay and NCCN guideline risk classification accuracy, they were still considered as highly cost-effective, in terms of the threshold defined by the World Health Organization (WHO).

In conclusion, 21-gene assay-guided treatment is considered to have cost saving and quality of life gain compared with NCCN guideline-guided treatment from a Chinese health care system perspective. The results of this study should inform better clinical decision making in China.

To my husband.

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CHAPTER 1

BACKGROUND

1.1 Breast Cancer

Breast cancer refers to a malignant tumor that starts in the cells of the breast, most commonly from either lobules or ducts.[1] The majority of breast cancer cases occur in women.[2] With more than 1.2 million new cases diagnosed every year worldwide, this is by far the most prevalent cancer among women.[3] In 2009, the estimated global costs of treating new cases of breast cancer reached US$ 24 billion, ranking third among all cancers.[4] At least 3.8 million years of life were lost (YLL) to breast cancer for women between the ages of 25 and 64 worldwide in 2000.[5] Thus, the burden of illness from breast cancer has become a global concern.

According to the WHO Cancer Fact Sheet 2008,[3] breast cancer incidence rates are high (greater than 80 per 100,000 women) in developed regions (except Japan) and low (less than 40 per 100,000 women) in most of the developing regions. For example, the incidence rate in China, within the Eastern Asia region, is around 25 per 100,000 women; while the U.S., within the Northern American region, has an incidence rate around 80 per 100,000 women, almost 3 times higher than the rate in eastern Asia.

Several possible explanations are available for this huge incidence difference across regions. First is race. Studies have shown that incidence differs between different

racial groups.[6,7] Even within the same region, for example, in the U.S., Whites have a much higher incidence rate, compared to Blacks, Asians and Hispanics.[2] Another issue is life style. Diet habits,[8-10] alcohol consumption,[11] age when first giving birth[12] and other life style factors are well-known risk factors for breast cancer. People share little in common on these factors among different regions.

However, other than the explanation from an epidemiology point of view, the incidence differences might also be due to the differences in life expectancy. In Africa, the female life expectancy is around 40-50 years[13]; many women may be dying before they get the chance to develop a breast cancer. In addition, in Western countries, many women have regular screening, either mammogram, clinical breast exam or breast self-exam. Yet, in developing countries, especially in rural areas, screening rates are incredibly low.[14,15] Since most breast cancer studies are done in Western countries with higher income and longer life expectancy, evaluation of interventions for detection and treatment in developing countries are lacking.

As to mortality rates, in both developing and developed countries, mortality rates are much lower than incidence rates, less than 20 per 100, 000 women.[3] This is due to early detection among Western countries and the high survival rate in early stage breast cancer (ESBC) patients. In the U.S., ESBC has a 5-year survival rate higher than 95%.[2] That is why early detection through screening is so important and why optimizing care for these patients has enormous potential for improving health care outcomes.

1.2 Early Stage Breast Cancer

1.2.1 Breast Cancer Stage

The TNM staging system is the most often used system to describe the growth of breast cancer. In this system, T describes the size of tumor and growth into nearby tissues, N tells if the cancer has spread to lymph nodes, and M indicates the extent of cancer in distant organs. Based on TNM categories, breast cancer is identified as stage I, stage II (IIA or IIB), stage III (IIIA, IIIB or IIIC), or stage IV. ESBC includes cancers in stages I, IIA, IIB, and IIIA; cancers that may have spread to nearby lymph nodes but not to distant parts of the body.[16]

There are four tumor features that are important to stage the cancer and decide the treatment[16,17]: (1) Tumor size – in early stage breast cancer patients, the tumor is usually smaller than 5 cm[16]; (2) Lymph node status – lymph node status, often abbreviated as LN+ or LN-, indicates whether the cancer has spread to nearby lymph nodes[16]; (3) Hormone receptor status – estrogen and progesterone are hormones in the body that start the growth of breast tissue. In some types of breast cancer, these hormones also help tumors to grow. These types of tumors are called estrogen receptor–positive (ER+), progesterone receptor–positive (PR+), or both. They tend to grow more slowly and are less likely to spread to the lymph nodes[16,18,19]; (4) HER2 (human epidermal growth factor receptor 2) status – if the cells are HER2 positive (HER2+), the growth of cancer cells is more likely to be rapid because there are more messages for the cell to grow and divide.[16,18,19]

1.2.2 Treatment for ESBC Patients

Different strategies are involved in ESBC treatment. For most women, surgery, either breast-conserving surgery or mastectomy, is the first step.[16,17] Breast-conserving surgery, which is less radical, consists of lumpectomy, which only removes the tumor and some surrounding tissue, while mastectomy removes the whole breast and possibly some of the lymph nodes. Both surgeries aim to remove the tumor. Both surgeries have similar survival and recurrence-free benefit for patient.[20]

After the surgery, patients usually receive further treatment to kill any cancer cells that might remain in the body and prevent the recurrence. Tamoxifen is the standard hormone therapy usually given to hormone receptor positive patients. However, a difficult and important decision for these patients is whether to undergo additional adjuvant chemotherapy. Studies have shown the likelihood of distant recurrence in patients treated with tamoxifen alone is about 15% at 10 years.[21] That is to say, at least 85 percent of patients would be over-treated with chemotherapy if it were offered to everyone. Although chemotherapy might add 4% absolute recurrence-free benefit for patients,[22] it is expensive and brings adverse events, such as infections, neutropenia, anemia, and nausea. Almost all chemotherapy patients undergo chemotherapy-related adverse events and more than 10% of them get a serious or life-threatening adverse event.[23,24] These adverse events will lead to more cost and poorer quality of life.

1.3 Risk Classification

To avoid unnecessary chemotherapy and adverse events, physicians need to classify the risk of recurrence for each patient. If the patient has high risk of recurrence,

they will provide the adjuvant chemotherapy, and if the patient is less likely to get recurrence, they will only give them the hormone therapy. Traditionally, risk classification relies on traditional guidelines based on clinical and pathologic tumor features as well as patient characteristics, including tumor size, hormone receptor status, HER2 status, and age of the patient. Free online software called Adjuvant!Online(AOL) is also available to assist the decision-making process. However, numerous studies have shown that physicians tend to overestimate the risk of cancer recurrence with these traditional tools and recommend adjuvant chemotherapy plus tamoxifen for most of the patients.[25]

Advances in genomics have led us to multiple molecular tools performed on an individual patient's tumor and tissue to achieve more accurate risk classification.[26] Among these tools, 21-gene assay is the only tool that has been studied in phase III trials and incorporated into major clinical guidelines. [16,27-29] Figure 1.1 shows the timeline for ESBC patients after incorporating 21-gene assay.

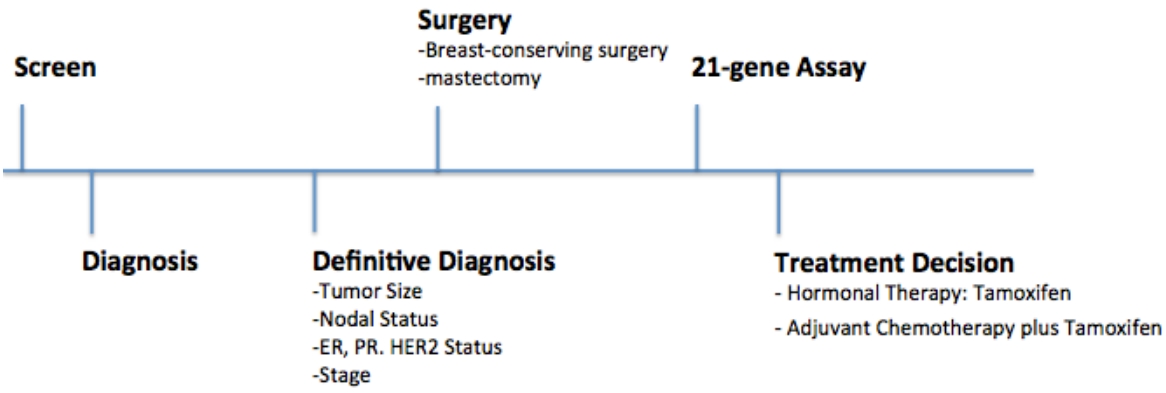

Figure 1.1 Timeline for early stage breast cancer patients

1.4 Twenty-one Gene Assay

The 21-gene assay (Oncotype DX® Breast Cancer Assay) is a reverse transcriptase-polymerase chain reaction (RT-PCR) assay, developed by Genomic Health Inc., Redwood City, CA. Performed on breast cancer tumor samples that were obtained from surgery, 21-gene assay analyzes the presence of specific mRNA for 16 cancer-related genes and 5 reference genes. After the assay, Recurrence Score (RS) predicting chemotherapy benefit, and the 10-year risk of distant recurrence is provided for the individual patient, ranging from 0 to 100. Then, patients can be classified into 3 recurrence risk categories: low risk (RS<18), intermediate (18<=RS<=30), and high (RS >30).[21]

A prospective study of archived tissue from 668 LN-, ER+ patients, the National Surgical Adjuvant Breast Cancer Project (NSABP) B-14 trial, has demonstrated the risk of distant recurrence at 6.8%, 14.3%, and 30.5%, for RS low, intermediate, and high group, respectively.[21] Another study of archived tissue from 651 LN-, ER+ patients, NSABP B-20 trial, compared chemotherapy plus tamoxifen with tamoxifen alone and demonstrated that the RS high group has the maximum benefit of 28% reduction in 10-year distant recurrence risk from adjuvant chemotherapy.[22]

More recently, TransATAC study proved the predictive value of 21-gene assay for LN+ patients[30] and SWOG-8814 study found the chemotherapy benefit for this subset of patients.[31] Japan had its own validation study among 200 LN- patients and 280 LN -/+ patients and found similar results.[32] Opened in January 2011, the RxPONDER Trial (Rx for Positive Node, Endocrine Responsive Breast Cancer) will evaluate chemotherapy benefits for 4,000 patients with LN+ breast cancer who have low to

intermediate RS results.[33] In addition, an international trial called TAILORx (Trial Assigning Individualized Options for Treatment (Rx)) is also ongoing to assess the chemotherapy benefit for RS intermediate patients.[34]

Based on the results of these clinical trials, 21-gene assay, as the only clinically validated multigene assay for breast cancer patients, is incorporated into 3 major clinical practice guidelines to provide prognosis information. Table 1.1 lists the recommendations regarding 21-gene assay in these three guidelines: NCCN (National Comprehensive Cancer Network),[16] ASCO (American Society of Clinical Oncology),[28] and St Gallen guidelines generated from the St Gallen International Breast Cancer Conference (2009).[27] They all support 21-gene assay as an option for LN-, ER+, HER2- ESBC patients to predict the benefit of chemotherapy.

Table 1.1 Recommendations regarding 21-gene assay in guidelines

NCCN Guidelines	Consider use in >0.5 cm, HR+, HER2- negative disease pT1, pT2, or pT3; and pN0 or pN1mi (<=2 mm axillary node metastasis)
ASCO Guidelines	Newly diagnosed patients with node-, ER+ breast cancer who will receive tamoxifen
St Gallen Consensus Guidelines	Predict chemotherapy benefit among patients with HR+, HER2- invasive disease

1.5 Cost-effectiveness problem

Studies have validated the effectiveness of 21-gene assay. Two published prospective studies indicated that 21-gene assay would improve the decision-making and change treatment recommendation in 31.5% and 32% of breast cancer cases, and most of the changes were from chemotherapy in addition to tamoxifen to tamoxifen alone (22.5% and 21%).[35,36] In addition, NSABP B-20 showed that the 21-gene assay will predict the magnitude of chemotherapy benefit.[22] However, compared with the free traditional prognostic tools, the cost of the test itself is expensive. In the U.S., the manufacturer suggested retail price is around $4,000.[37] In the cost-effectiveness plane shown in Figure 1.2, the situation falls into the I Quadrant, which indicates higher cost, better outcome, and a positive ICER. Thus, with the huge cost saving from avoiding unnecessary chemotherapy and the expensive price of 21-gene assay itself, a cost-effectiveness question arises.

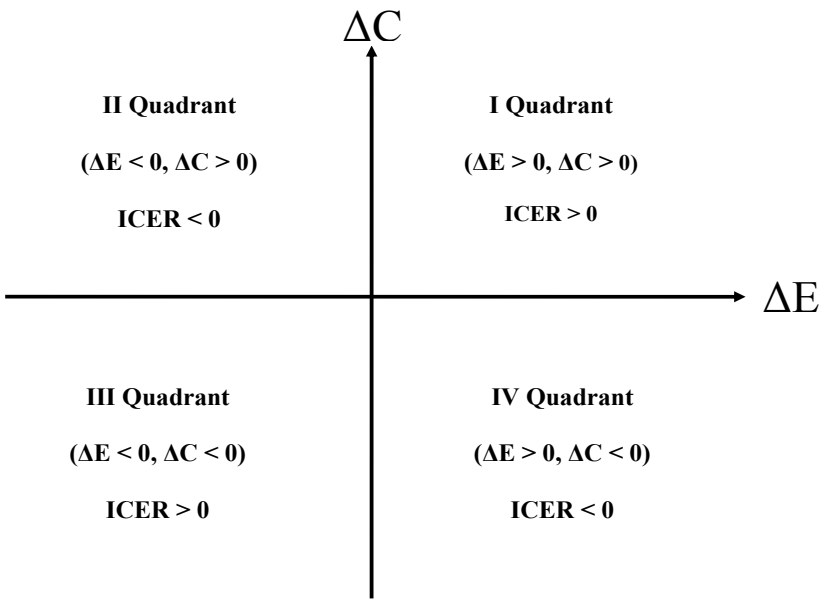

Figure 1.2 Cost-effectiveness plane

1.6 CEA Studies Conducted So Far

To solve this cost-effectiveness problem, economic evaluations of 21-gene assay have been reported from North American,[37-42] South American,[43] European,[44] and Asian countries.[32,45,46]

1.6.1 Example Model

Figure 1.3 is a CEA example model, done by Hornberger in 2005, and several later studies developed their models based on this study.[32,37,46] In this model, patients were assigned to the 21-gene assay testing group and no 21-gene assay group. Both groups received NCCN guideline risk classification first. The 21-gene assay group underwent a reclassification into either RS intermediate/high group or RS low group. Patients received different chemotherapy based on their HER2 receptor status. All patients who received chemo went into a toxicity subtree and then go to the outcome subtree. All patients that did not receive the chemo directly go to the outcome subtree.

1.6.2 Comparison of Studies

By 2011, 11 CEA studies had been conducted to evaluate the economic impact of 21-gene assay; all were modeling studies performing decision trees or Markov models. Table 1.2 lists these 11 studies. Five of them were studies in the U.S., while UK, Canada, Brazil, and Israel each had one. Two studies were done in Japan, one based on the U.S. validation study[46] and one based on the Japanese validation study.[32] Brazil is the only developing country conducting a CEA study on this topic.

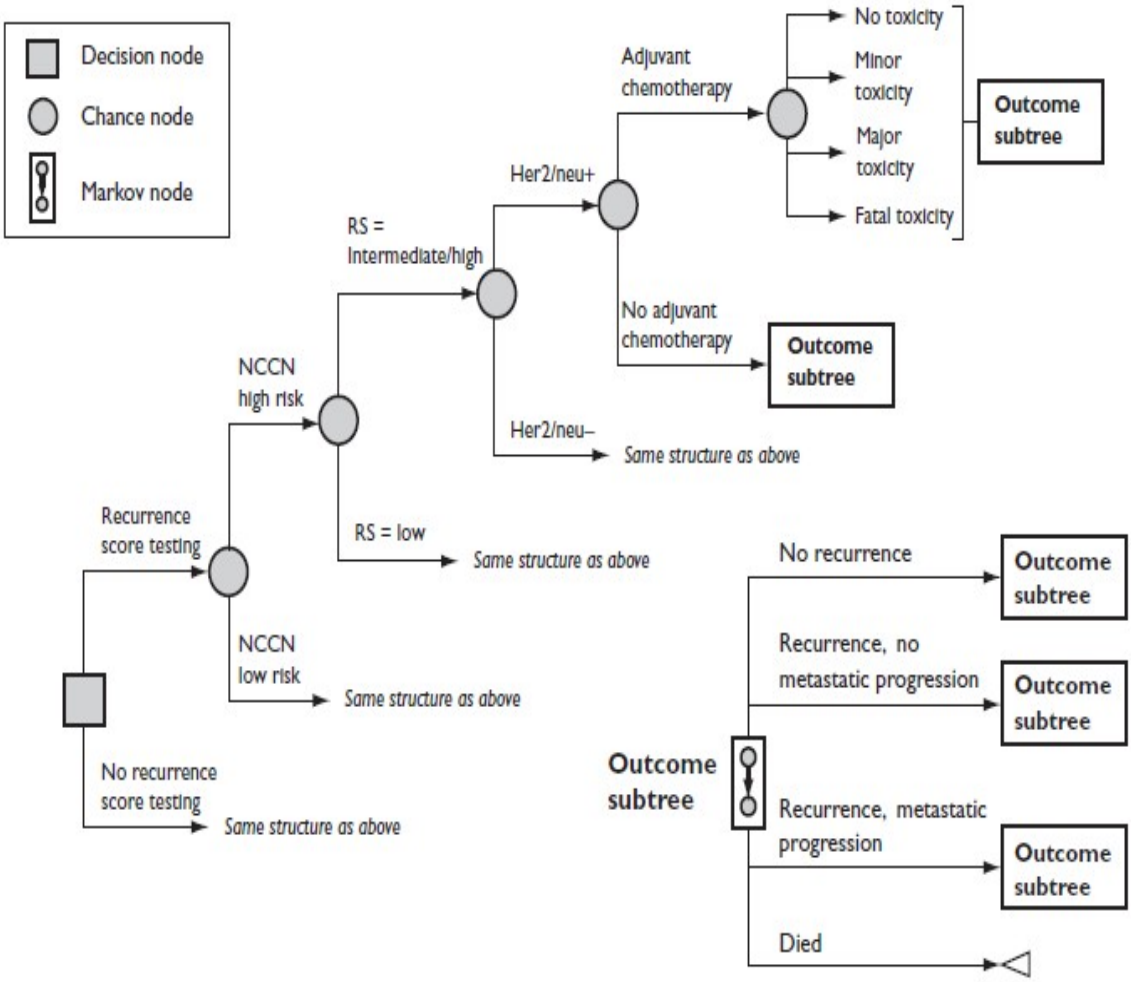

Figure 1.3 Example model of CEA study for 21-gene assay[39]

Hypothetical cohorts are analyzed as the base case in studies, expect for Hornberger et al. (2011).[37] Different age and clinical characteristics were chosen as the base case. According to the validation trial, the study was based on mean age at diagnosis of breast cancer in the particular country. Different prognosis tools were chosen as alternatives for the comparison according to standard clinical practice in the particular country. Meta-analysis results of six published studies on the decision impact of 21-gene assay were selected as alternatives for Hornberger et al. (2011).[37]

Table 1.2 CEA studies for 21-gene assay

Article	Country	Comparing group	Base Case
Hornberger et al. 2005	U.S.	NCCN	LN-, ER+, HER2-/+, ESBC
Lyman et al. 2007	U.S.	1.Tamoxifen 2. Adjuvant therapies	LN-, ER+, HER2-, ESBC
Kondo et al. 2008	Japan	1. NCCN 2. St Gallen	55-year old LN-, ER+, HER2-/+, ESBC
Cosler et al. 2009	U.S.	1.Tamoxifen 2. Adjuvant therapies	LN-, ER+, HER2-, ESBC
Bacchi et al. 2010	Brazil	Web-based survey of 30 Brazilian oncologists	Hypothetical cohort of 100 patients based on tumor size
Tsoi et al. 2010	Canada	AOL	50-year old women with LN-ER+ HER2- ESBC
Klang et al. 2010	Israel	Traditional prognostic pathways	LN-, ER+, HER2-, ESBC
Hall et al. 2011	UK	Adjuvant therapies	LN+, ER+, HER2-, ESBC patients with chemotherapy
Kondo et al. 2011	Japan	St Gallen 2009	55-year old 1.LN-, ER+, ESBC 2.LN-/+, ER+, ESBC
Vanderlaan et al. 2011	U.S.	NCCN	Disease free case (hypothetical cohort of 2 million with age distribution of US population)
Hornberger et al. 2011	U.S.	Meta-analysis results	Real World Data

1.6.3 Results of Studies

The majority of studies reported an ICER falling into the range between 2,000 and 10, 000 USD and concluded that 21-gene assay is considered cost-effective, as shown in Table 1.3. For example, Kondo et al. (2011)[32] estimated an ICER of US$3,848 perQALY for the indication for LN- scenario and $5,685 per QALY for the indication for LN-/+ scenario, U.S. dollars year 2010 value. Both are not more than the suggested social willingness-to-pay for one QALY gained from an innovative medical intervention in Japan (US$50,000/QALY). Tsoi et al. (2010)[42] reported an ICER of $61,800 per QALY, Canadian dollars year 2008 value. And according to the willingness to pay thresholds of $50,000 to $100,000 per QALY in Canada, 21-gene assay is still considered as cost-effective.

Other studies, such as Bacchi et al. (2010),[43] reported a cost saving of $79,361 for 100 Brazil breast cancer patients, varying by tumor size, U.S. dollars year 2010 value.

1.7 Gap

All eleven studies found 21-gene assay cost-effective or cost saving; however, none of these studies were done in China. Differences in epidemiology, treatment, and healthcare system between the U.S. and China are compared here to illuminate the importance of CEA study regarding 21-gene assay in China and why the results from the U.S. and other developed countries cannot be generalized to China.

Table 1.3 Results of CEA studies for 21-gene assay

Article	Country	ICER	Conclusion
Hornberger et al. 2005	U.S.	N/A	Cost-effective for RS intermediate/high group and cost saving for RS low group
Lyman et al. 2007	U.S.	$4,432	Cost-effective compared to chemotherapy and tamoxifen alone
Kondo et al. 2008	Japan	$26,065/$10,744	Compare to NCCN and St Gallen, 21-gene assay is cost-effective
Cosler et al. 2009	U.S.	$3,385	Cost-effective
Bacchi et al. 2010	Brazil	N/A	21-gene assay is cost saving in Brazil, vary by tumor size
Tsoi et al. 2010	Canada	$63,064	21-gene assay is cost-effective in Canada
Klang et al. 2010	Israel	$10,770	21-gene assay is cost-effective in Israel.
Hall et al. 2011	UK	$8,852	21-gene assay –directed chemotherapy is cost-effective
Kondo et al. 2011	Japan	$3,848/$5,685	For both LN- and LN-/+, 21-gene assay is cost-effective
Vanderlaan et al. 2011	U.S.	N/A	For N+(1-3)/ER+ HER2- patients, 21-gene assay is cost saving
Hornberger et al. 2011	U.S.	N/A	21-gene assay is cost saving patients enrolled with Humana

1.7.1 Epidemiology Differences

As listed in Table 1.4, approximately 20 women per 100,000 are diagnosed with breast cancer each year in China.[47] Although the incidence rate is 6 times less than the rate in the U.S., the total number of cases is large, both among the highest in the world. In 2000, the China National Office for Cancer Prevention and Control reported an increasing incidence rate of 37% and an increasing mortality rate of 38.9% over 10 years in the major cities.[48]

In the U.S. there is only a slightly increasing incidence rate trend between 2005 and 2008 and a consistently decreasing mortality rate from 1990 to 2008.[2] These all indicate the tremendous public health burden and the huge potential saving by treating the patients with breast cancer cost-effectively in China.

Moreover, characteristics of the disease in the Chinese population also differ from the U.S. (Table 1.5). Women with newly diagnosed breast cancer are more likely to be premenopausal and are 17 years younger at diagnosis compared to developed countries.[2,47] There are 19% less ER+ and 6.5% less HER2- patients in China.[2,47] Since ER+ and HER2- refer to less aggressive breast cancer progression, lower ER+ and

Table 1.4 Epidemiology differences between U.S. and China

	Incidence rate*	Mortality rate*	Incidence case	Incidence trend	Mortality trend
U.S.	124.0	23.5	230,480	+0.7 (2005-2008)	-2.2(1990-2008)
China	20	5.5	190,000	+3.7 yearly	+3.9 yearly

Per 100,000 women
Source: SEER Cancer Statistics[2]; Li et al. 2011[47]; He et al. 2011[49]; Zhong Guo Ru Xian Ai Diao Cha Bao Gao, 2010[48]

Table 1.5 Patients' demographic differences between U.S. and China

	Mean age at diagnosis	Premenopausal	ER+	HER2-	5-year survival rate
U.S.	62	N/A	75%	80%	89.1%
China	45	62.9%	56%	73.5%	Increasing from 50%

Source: SEER Cancer Statistics[2]; Li et al. 2011[47]

HER2- proportions indicate China has more severe breast cancer. Although the 5-year survival rate of breast cancer in China is increasing from 50% since the 1960s, it is still much lower than the 89.1% in the U.S.[2,47] According to the WHO health statistics 2009, women in the U.S. and China share a similar life expectancy at birth.[13] Thus, with younger patients, more aggressive disease, and a lower survival rate, the life-year loss among breast cancer patients in China is tremendous.

1.7.2 Treatment Differences

Table 1.6 lists the treatment differences between the U.S. and China. Oncologists are following different guidelines in the two countries. In the U.S., multiple guidelines are available, such as NCCN, St Gallen, and ASCO. However, the only available breast cancer treatment practice guideline used in China is the NCCN Chinese Version, which is a translation version of the NCCN in the U.S., updated to 2011, and adjusted by Chinese oncologists based on their opinion and practice experience to fit in China.[50-52] For example, for the LN-, ER+, HER2- subset of ESBC patients, U.S. guidelines support the new evidence and recommend doxorubicin/cyclophosphamide followed by weekly paclitaxel (AC+T) as the standard regimen,[16,53] while NCCN Chinese Version

Table 1.6 Treatment differences between U.S. and China

	Guideline	Chemotherapy	Chemo regimen[a]	21-gene assay
U.S.	Multiple	Around 60%	AC+T	Recommended
China	NCCN Chinese Version	81.4%	AC or TC	Not recommended

[a]adjuvant therapy for LN-, HR+, HER2- patient
Source: NCCN breast cancer guideline V1.2012[16]; NCCN breast cancer guideline Chinese Version 2011[50]; Li et al. 2011[47]

still recommends doxorubicin/cyclophosphamide (AC) or docetaxel/cyclophosphamide (TC).[50]

Oncologists in China provide chemotherapy to most breast cancer patients, leading to around 20% more patients undergoing chemotherapy, compared with the U.S.[16,47] Meanwhile, 21-gene assay is removed from NCCN Chinese Version for its expensive price and lack of prospective study results.[50,54]

1.7.3 Chinese Health Care System

Limited resources are also a concern in China. The increasing size of the population has been a burden to the whole country and, of course, has influenced the quality of health care each person obtains.[55,56] Table 1.7 lists numbers of healthcare resources between the two countries. It is not hard to see the huge shortage of healthcare resource in China relative to the US. For instance, the ratio of nurses and physicians is almost equal in China, about 1 each per 1,000 residents.[55,57] Yet, others have found a lower ratio of nurses to physicians.[58] In contrast, the US has approximately 4 nurses

Table 1.7 Healthcare resource differences between U.S. and China

Country	Total expenditure on health as % of GDP, 2006	Per capita total expenditure on health, 2006 ($)	Doctors, 2000-2007 (per 10,000 population)	Nurses and midwives, 2000-2007 (per 10,000 population)	Hospital beds (per 10,000 population)
China	4.6	216	14	10	22
United States	15.3	6719	26	94	31

Source: World Health Organization, 2009[55,57]; Ungos et al. 2009[58]

for every physician and 9.4 nurses per 1,000 population. Compared with U.S. patients, Chinese patients are spending much less money on healthcare and getting fewer doctors, fewer nurses, and limited hospital beds.[55-58] This shortage will definitely influence the resource utilization when breast cancer patients are treated.

China also has a unique insurance system, consisting of the New Cooperative Medical System for rural residents; employee insurance and resident insurance for urban citizens; and supplemental insurance as a government employee benefit, catastrophic coverage, and commercial insurance.[59] Co-pay for different insurance type varies. The rural insurance program only covers 50% of the healthcare expenditure while urban insurance coverage usually goes up to 85%. Government employees receive full coverage. An entitlement program for elderly residents similar to Medicare in the U.S. is not available in China.[59,60]

1.8 Objective of the Study

With these huge differences in epidemiology, treatment, and healthcare system, we cannot easily generalize the results from the U.S. and other developed countries to China. Although the cost-effectiveness of 21-gene assay in developed countries is well established, the potential economic impact of incorporating the 21-gene assay in China is still unknown. To understand the use of the 21-gene assay and whether it leads to better health outcomes, economic evaluation from the Chinese health care system's perspective is needed. Hence, this study aims to perform a cost-effectiveness analysis of 21-gene assay on treatment of ESBC patients in China.

CHAPTER 2

METHODS

A cost-effectiveness analysis with a decision tree and Markov model was performed based on the validation studies of 21-gene assay and published literature. Costs were estimated under the Chinese health care system with a sensitivity analysis, from the health care provider's perspective. The model and all analyses were performed using TreeAge Pro 2012 Suite (TreeAge, Williamson, MA).

2.1 Base Case

A hypothetical cohort of 10,000 female patients with LN-, ER+, HER2- early stage breast cancer at the age of 45 after either breast-conserving surgery or mastectomy were chosen as the base case. Age 45 was chosen according to the average age of women with a new breast cancer diagnosed in China.[47] Women with LN-, ER+, HER2- early stage breast cancer were chosen based on the population recommendations for the 21-gene assay in major guidelines in United States.[16,27,28]

Two scenarios were set up in this model for these patients: continue with NCCN Guideline Chinese Edition guided treatment, or receive the 21-gene assay RS guided treatment. NCCN Guideline Chinese Edition was chosen as the alternative because it is widely adopted in most hospitals in China.[52]

2.2 Decision Tree and Markov Model

Figure 2.1 shows the decision tree in this model. In the 21-gene assay scenario, patients received risk classification by NCCN criteria first, followed by reclassification using 21-gene assay RS. In the NCCN scenario, patients only followed the NCCN guideline for risk classification. Based on the recommendation in major guidelines, RS intermediate-risk patients were grouped together with the RS high-risk patients. An assumption was made that 100% of patients who fall in this group would undergo adjuvant chemotherapy; similarly, 100% of patients in the high-risk group by NCCN criteria would receive chemotherapy. Low-risk patients would not receive chemotherapy. Patients receiving chemotherapy may experience no toxicity, grade 1-2 toxicity, grade 3-4 toxicity, or fatal toxicity.

The Markov model in Figure 2.2 shows the health states once the adjuvant therapy or hormone therapy is completed. Four stages are considered here: (1) disease-free stage with no recurrence, which may progress to local recurrence stage, distant/metastatic recurrence stage; (2) local recurrence stage, which may transition back to a disease-free stage after surgery or progress to distant recurrence; (3) metastatic disease, which is currently not curable and therefore can only transition to (4) death.

The cycle length of each stage was defined as 1 year. Since we calculated the probabilities of recurrence transit between stages from 10-year distant recurrence-free survival ($DRFS_{10}$) and the fact that most of the recurrences occur within this time period, the Markov model was repeated up to 10 years.

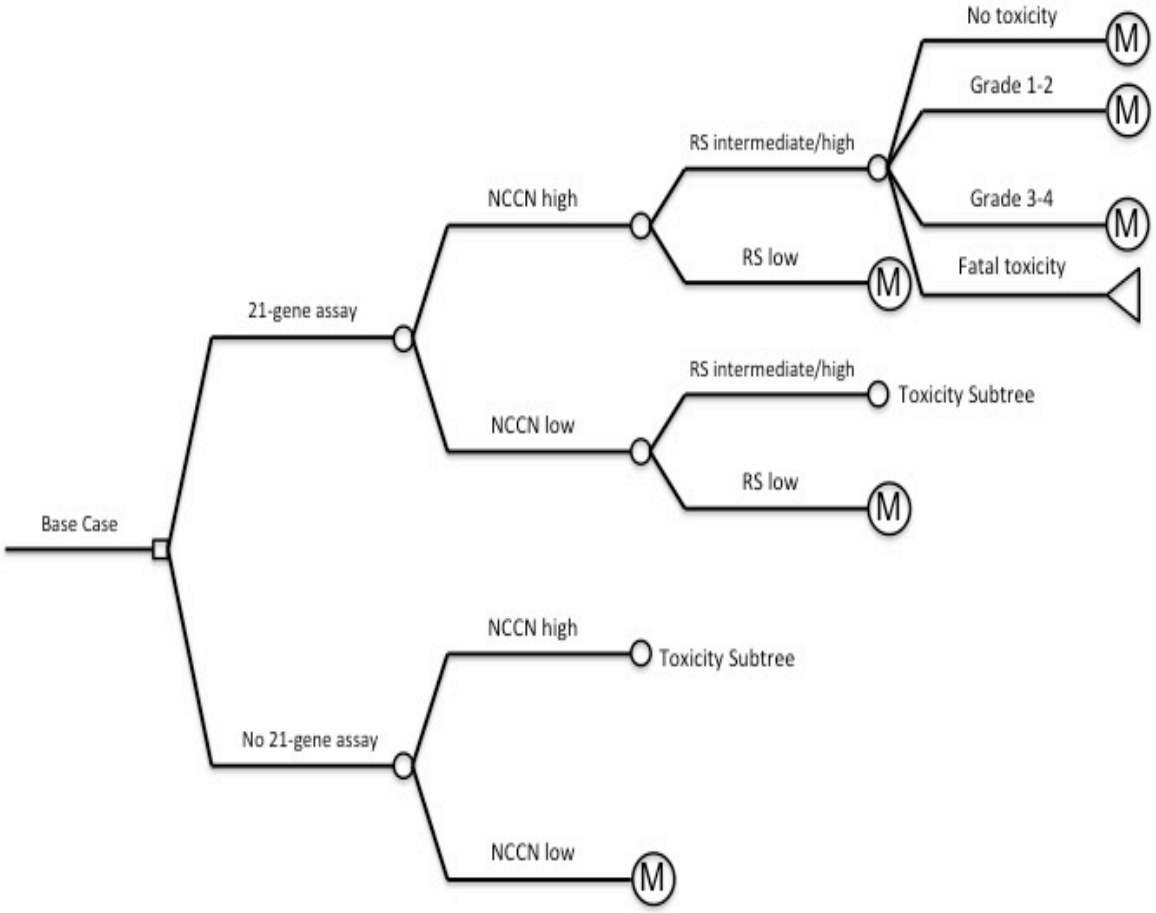

Figure 2.1. Decision tree

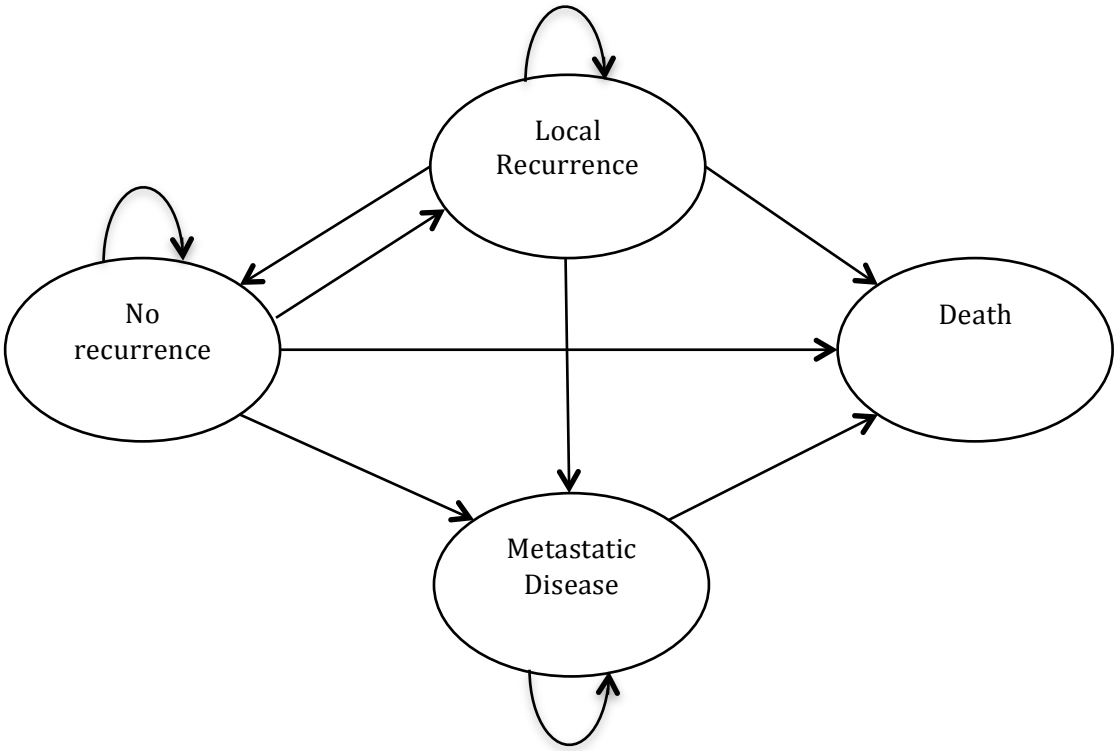

Figure 2.2. Markov health states

2.3 Probability of Risk Classification

Data on probabilities of risk classification using NCCN criteria and/or 21-gene assay were derived from NSABP B-14 clinical trial (Table 2.1).[21] For the 7.9% of patients who fall into the low-risk group by NCCN criteria, 28% were reclassified into the intermediate/high group by 21-gene assay; for the 92.1% patients who were assigned to the high-risk group by NCCN criteria, 49% were reclassified into the low group according to 21-gene assay RS.

Table 2.1 Probabilities of risk classification

	Probability (%)		Probability (%)[a]
NCCN criteria		21-gene assay	
Low risk	7.9	Low	5.7
		Int/high	2.2
High risk	92.1	Low	44.9
		Int/high	47.2

Int/high: intermediate or high
[a] Probabilities in this column add up to reflect the probabilities in NCCN group.
Source: NSABP B-14[21]

2.4 Probability of Toxicity from Chemotherapy

Toxicity profiles were adapted from the National Cancer Institute Common Toxicity Criteria.[61] Based on these criteria, grade 1-2 toxicity refers to mild to moderate severity adverse events – no or minimal intervention needed; grade 3-4 toxicity refers to severe to life-threatening adverse events – hospitalization needed and limiting self-care activities of daily living; and grade 5 refers to fatal toxicity related to adverse events.

According to the NCCN Guideline Chinese Edition 2011,[50] doxorubicin/ cyclophosphamide (AC) and docetaxel/cyclophosphamide (TC) are the two recommended standard regimens as adjuvant therapy for lymph-node negative and hormone-receptor positive breast cancer patients. Jones et al. (2006)[24] stated that TC has similar overall toxicities compared to AC, based on the number of patients in each toxicity grade. Thus, AC and TC were assumed to have the same toxicity profile and AC was chosen as the base case chemotherapy regimen to perform analysis in our model. The probabilities of different toxicity measures were obtained from published literature from phase 3 randomized clinical trials of AC.[23]

2.5 Risk of Recurrence and Death

Annual risks of recurrence and survival in different risk classifications were derived and calculated from probability of 10-year recurrence rate reported from published meta-analysis of clinical trials.[62] (Table 2.2) The proportion of local recurrence among all recurrence events was 18.75% according to Liubao et al. (2009).[51] A further 30% relative risk reduction of recurrence associated with adjuvant chemotherapy plus tamoxifen versus tamoxifen alone were applied for NCCN high-risk patients; and for RS intermediate/high-risk patients, 45% relative risk reduction was applied.[39]

Since the AC regimen was the base case regimen, the risk of recurrence derived from the literature reflected the recurrence rate of the AC regimen; and the probabilities of recurrence for the TC regimen were estimated by multiplying the probabilities for AC by hazard ratio derived from the results of ACTC trial.[24,53]

Once patients developed recurrence, it was assumed that the transition probabilities were identical in all patients, regardless of their risk group and treatment. The probabilities of local recurrence to distant recurrence were adapted from the meta-analysis results from Liubao et al. (2009).[51] The average life-span for patients developing distant recurrence is 21 months. For non-breast cancer related death, the probabilities were derived from 2009 life tables for Chinese women from the WHO.

2.6 Utilities

A utility weight was assigned to each health state as an estimate of the quality-adjusted life-year (QALY) gains. Perfect health is expressed as a utility weight of 1;

Table 2.2 Transition probabilities

	Base case value	Range tested in sensitivity analysis
Probability of distant recurrence by 10 years[62]		
NCCN low	7.8%	Change by ±50%
NCCN high	21.9%	Change by ±50%
Relative risk reduction with chemotherapy		
NCCN high[39,42]	30%	95% CI
RS int/high[39,62]	45%	95% CI
Probability of chemotherapy toxicity[23]		
Grade 1-2	68.5%	Change by ±50%
Grade 3-4	27.3%	Change by ±50%
Fatal	0.1%	Change by ±50%
Hazard ratio for TC, compared to AC[24,53]	0.74	95% CI
Probability of death		
Average length of life in patients developed distant recurrence[59,63]	21 months	Change by ±50%
Non-breast cancer death over 10 years[55]	Based on statistical life table of Chinese women, 2009	Change by ±50%
Probability of local recurrence if recurrence occurs[24,51]	18.75%	Change by ±50%
Probability of local recurrence to distant recurrence[51,64-66]	Based on published literature	Change by ±50%

poorer quality of life leads to lower utility while death is represented as 0 weight. Utilities were derived from published literature[67-70] and the Tufts/Harvard cost-effectiveness analysis registry[71] (Table 2.3).

As shown in Table 2.3, the utility weights associated with chemotherapy without toxicity, chemotherapy with grade 1-2 toxicity, and chemotherapy with grade 3-4 toxicity were assumed as 0.74, 0.70, and 0.60, respectively. For the no recurrence state, the local recurrence state, and the distant recurrence state, the utilities each year as they stayed in the state were 0.90, 0.70, and 0.50, respectively.

Table 2.3 Utilities weight

	Base case value	Range tested in sensitivity analysis
Toxicity		
No toxicity[68-71]	0.74	Change by ±20%
Grade 1-2[67]	0.70	Change by ±20%
Grade 3-4[67]	0.60	Change by ±20%
No recurrence[68,70,71]	0.90	Change by ±20%
Local recurrence[68,70,71]	0.70	Change by ±20%
Distant recurrence[68,70,71]	0.50	Change by ±20%
Death[68,71]	0	0

2.7 Costs

2.7.1 Perspective

This study was from a Chinese health care provider perspective, thus, only direct medical costs were considered. Direct nonmedical costs such as transportation and indirect costs such as loss of productivity were excluded. All costs were expressed in Chinese Yuan (CNY), 2008 value and translated to U.S. Dollar (USD) at the rate of $1 = 6.834 CNY, as of January 2009. A 3% discount rate per year was applied to all costs.

2.7.2 Cost Estimation of 21-gene Assay

Since manufacturer's suggested retail price for 21-gene assay in China is not available, its price was estimated according to the differences between chemotherapy drug costs in China and the U.S.

As to the sensitivity analysis range of the cost of 21-gene assay, since 50% upper and lower bounds does not span the retail price ($3 975, effective July 1, 2009) in the U.S.,[39] a wider range, CNY4 043 to CNY 27 165 ($591 to $3 975), was utilized to cover the lower 50% bound of the estimated price in China and its retail price in the U.S.

2.7.3 Costs input

The major cost inputs in this study were derived from Liubao et al. (2009),[51] including costs associated with chemotherapy, chemotherapy toxicity, recurrence treatment, and follow-up and end-of-life health care (Table 2.4). This was a cost-effectiveness study comparing the TC and AC regimen in early stage breast cancer patients from a Chinese health care provider perspective. All costs data and resource utilization information were collected from the Second Xiangya Hospital of Central South University in Changsha, China. This is one of the most famous and first-class hospitals in China. In Hunan Province, about one-third of breast cancer patients were treated in this hospital. In addition, oncologists in this hospital follow the Chinese edition of the NCCN Guidelines.[51] Thus, costs from this study were chosen as the base case. In China, an economic gap exists among the different geographical areas, so we addressed this issue in the sensitivity analysis.

The costs of chemotherapy included cost of the chemotherapy agents, administration, and supportive treatments. Three days of hospitalization for each cycle and body surface area of 1.6 m^2 representing the average Chinese woman's body size were used. The drug acquisition for regimens were: AC, Doxorubicin 60 mg/m^2, Cyclophosphamide 600 mg/m^2, every 21 days for 4 cycles; TC, Docetaxel 75 mg/m^2, Cyclophosphamide 600 mg/m^2, cycled every 21 days for 4 cycles. Again, cost of the AC regimen was the base case. The cost of grade 1-2 toxicity was included in the costs of chemotherapy treatment. The cost of grade 3-4 toxicity incorporated hospitalization, management, and medication costs of grade 3-4 toxicity events (nausea and vomiting, febrile neutropenia and neutropenia) per cycle. Based on the NCCN Guideline, the cost

Table 2.4 Costs (Chinese Yuan, year 2008 values)

	Base case value	Range tested in sensitivity analysis
21-gene assay (Oncotype DX)	8 086	4 043 ~ 27 165
Tamoxifen/per year[51]	638	Change by ± 50%
Chemotherapy/per cycle		
AC[51]	2 021	Change by ± 50%
TC[51]	5 742	Change by ± 50%
Treatment for toxicity/per cycle		
Grade 3-4[51]	2 427	Change by ± 50%
Treatment for local recurrence/per year[51]	82 730	Change by ± 50%
Treatment for distant recurrence/per year[51]	93 660	Change by ± 50%
Follow-up for disease-free/per year[51]	1 846	Change by ± 50%
Follow-up for local recurrence/per year[51]	1 846	Change by ± 50%
Follow-up for distance recurrence/per year[51]	78 050	Change by ± 50%
Terminal 3 month[51]	39 179	Change by ± 50%
Discount rate	3%	0 to 5%

of tamoxifen was applied to all patients for 5 years or until the development of distant recurrence or death. The costs of treatment for recurrence, follow-up, and terminal care were obtained from selected patients from Second Xiangya Hospital of Central South University.

2.8 Outcomes

The model estimated the total direct health care costs and QALY for 21-gene assay guided treatment and NCCN guideline guided treatment, and also the incremental cost per QALY gained – incremental cost-effectiveness ratio (ICER). ICER was calculated as the difference in total cost divided by the difference in QALYs between the two treatment strategies.

$$\text{ICER} = \frac{Cost\ (21-gene\ assay-guided\ treatment) - Cost\ (NCCN-guided\ treatment)}{Effect\ (21-gene\ assay-guided\ treatment) - Effect\ (NCCN-guided\ treatment)}$$

2.9 Sensitivity Analysis

In order to assess the robustness of the results obtained from the model, one-way sensitivity analysis was performed on all variables. The ranges used in the one-way sensitivity analysis were derived from a review of the existing literature. In the case of a lack of data, a range of 50% lower and upper bound was considered for the cost variables and 95% confidence interval as the range was considered for the clinical variables.

In particular, the starting age of the cohort was varied from 35 to 55 years old; relative risk reductions and hazard ratio for TC adopted the 95% confidence interval range, while the rest of the probabilities were changed by ± 50%; following Kondo et al. 2008, utility weights were all varied by ± 20%; costs were all varied by ± 50%, except for the cost of 21-gene assay; the discount rate was changed from 0 to 5%.

Tornado diagrams were used to assess the importance and possible influence of the choice ranges for sensitivity analysis.

CHAPTER 3

RESULTS

Results of the decision tree and Markov model are displayed in the following section. Base case cost-effectiveness analysis was performed first, followed by one-way sensitivity analysis to test the robustness of the model. A tornado diagram is presented to demonstrate the result of the sensitivity analysis and stability of the ICER. At the end, the model was rerun by replacing the cost and recurrence rate of base case chemotherapy with AC by TC regimen.

3.1 Cost-effectiveness

Table 3.1 shows the results of the base case cost-effectiveness analysis of 21-gene assay-guided treatment, among LN-, ER+, HER2-, early stage breast cancer Chinese patients. The total cost of the 21-gene assay-guided treatment in a 45-year-old patient was estimated as ￥87 786 (US$12 845), compared with the NCCN-guided treatment of ￥98 912 (US$14 473), which results in a cost saving of ￥11 125 (US$1 628). The 21-gene assay-guided treatment was associated with a QALY of 8.63 year, compared with a QALY of 8.33 year for the NCCN-guided treatment, with an incremental QALY of 0.30 year. The ICER of the NCCN-guided treatment versus 21-gene assay treatment is dominated, with a value of -37 141 ￥/QALY (5 435 US$/QALY), which means 21-

Table 3.1 Results of cost-effectiveness analysis

Treatment strategy	Cost (￥)	Incremental cost (￥)	Effect (QALY)	Incremental effect (QALY)	ICER (￥/QALY)
21-gene assay-guided	87 786	-11 125	8.63	0.30	Dominant
NCCN-guided	98 912		8.33		

Abbreviation: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

gene assay-guided treatment is less expensive and more effective than NCCN-guided treatment.

3.2 Sensitivity Analyses

The results of the one-way sensitivity analysis are shown in Figure 3.1. Twelve variables are listed by the order of magnitudes of the ICER range. The model results were not sensitive to variables not listed in the figure.

Twenty-one gene assay-guided treatment is cost saving and more effective for most of the variables, with three exceptions: (1) cost of 21-gene assay; (2) probability of being assigned to a high-risk group based on NCCN guideline criteria; (3) probability of 10-year recurrence rate for NCCN high-risk group patients. If the cost of 21-gene assay in China equals the retail suggested price in the U.S. (￥27 165, US$3 975), then the 21-gene assay-guided treatment will be cost increasing; the cost per QALY gained would be ￥26 551 (US$ 3 885). If only 46.1% of patients (50% of the base case) were classified into the high-risk group, the 21-gene assay-guided treatment would still be more effective but with higher total cost, with an ICER of 21 572 ￥/QALY (3 156

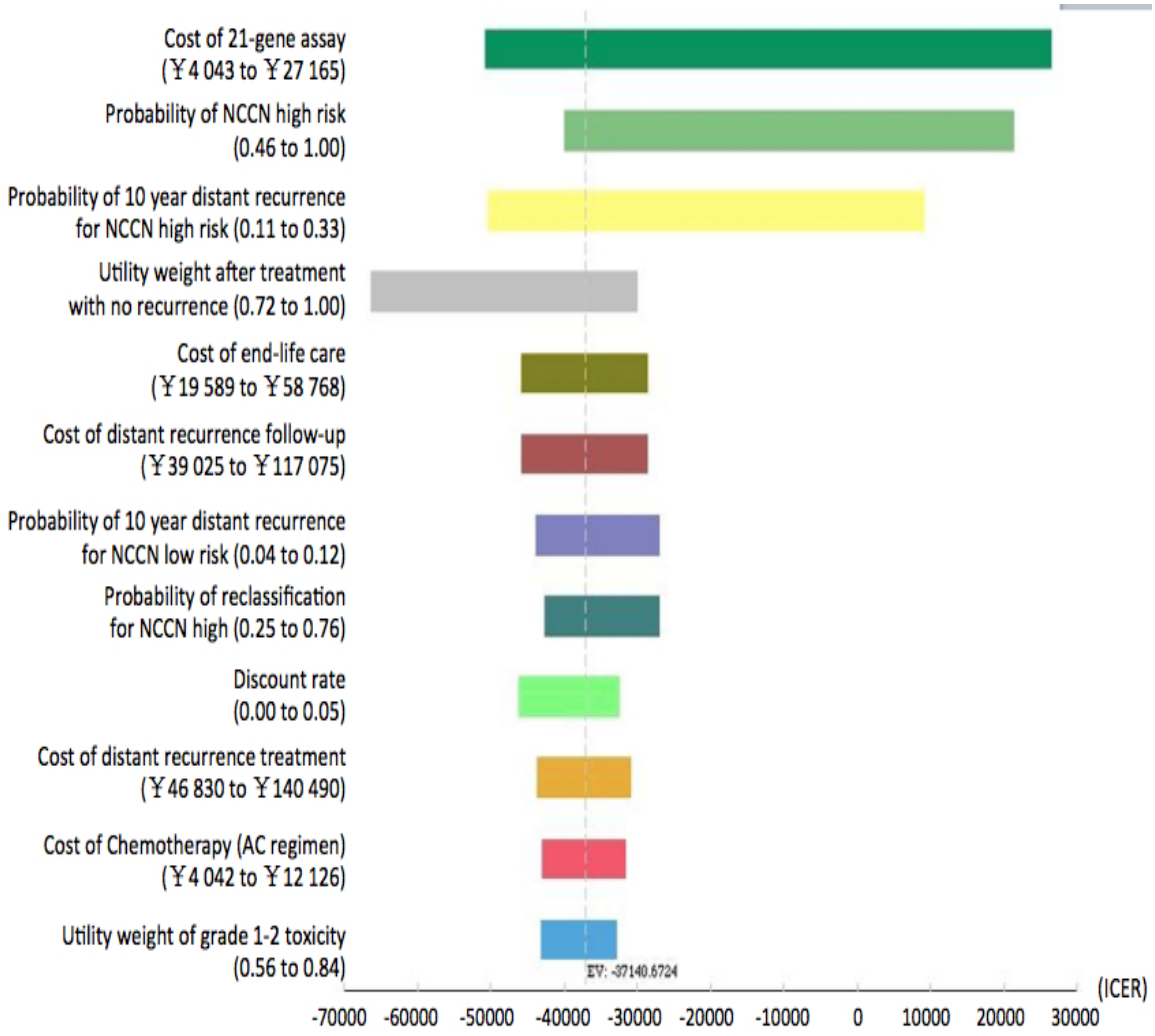

Figure 3.1 Results of sensitivity analyses

US$/QALY). Probability of 10-year distant recurrence calculated based on $DRFS_{10}$ also had a large impact on the results. If NCCN high-risk patients had a lower probability of 10-year distant recurrence, 11% vs. 50% in the base case, the 21-gene assay-guided treatment would be QALY gained and cost increasing, with an ICER of 9 218 ￥/QALY (1 349 US$/QALY).

Twenty-one gene assay is dominant for other variables, including other cost inputs, other probability inputs, utility weights, discount rate, and patient age at diagnosis.

3.3 Results for TC Regimen

After rerunning the model by changing the chemotherapy regimen to TC, similar results were obtained (Table 3.2, Figure 3.2). Compared to the base case using the AC chemotherapy regimen, TC regimen resulted in a larger cost-saving Y13 285 (US$ 1 934) and less benefit gain of 0.24 QALY for the 21-gene assay-guided treatment. NCCN-guided treatment is still dominated by 21-gene assay treatment with a negative ICER (-54 566￥/QALY, 7 984 US$/QALY).

In sensitivity analysis with TC regimen, only the cost of 21-gene assay and probability of being in the high-risk group based on NCCN guideline criteria would change the sign of the ICER. Similarly to analysis with the AC regimen, having the U.S. retail price as the cost of 21-gene assay would result in a higher expenditure for 21-gene assay-guided treatment and the cost per QALY would be ￥23 795 (US$3 482). Compared with analysis with AC regimen, the probability of being high-risk by NCCN criteria became a more sensitive variable with a larger range in the TC model; the cost per QALY would be ￥33 429 (US$4 891) if probability were changed to 46.05%.

In both analysis with the AC regimen and the TC regimen, results are consistent that 21-gene assay-guided treatment is either cost-effective or dominates NCCN-guided treatment.

Table 3.2 Results of cost-effectiveness analysis with TC regimen

Treatment strategy	Cost (￥)	Incremental cost (￥)	Effect (QALY)	Incremental effect (QALY)	ICER (￥/QALY)
21-gene assay-guided	86 692	-13 285	8.74	0.24	Dominant
NCCN-guided	99 978		8.50		

Abbreviation: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

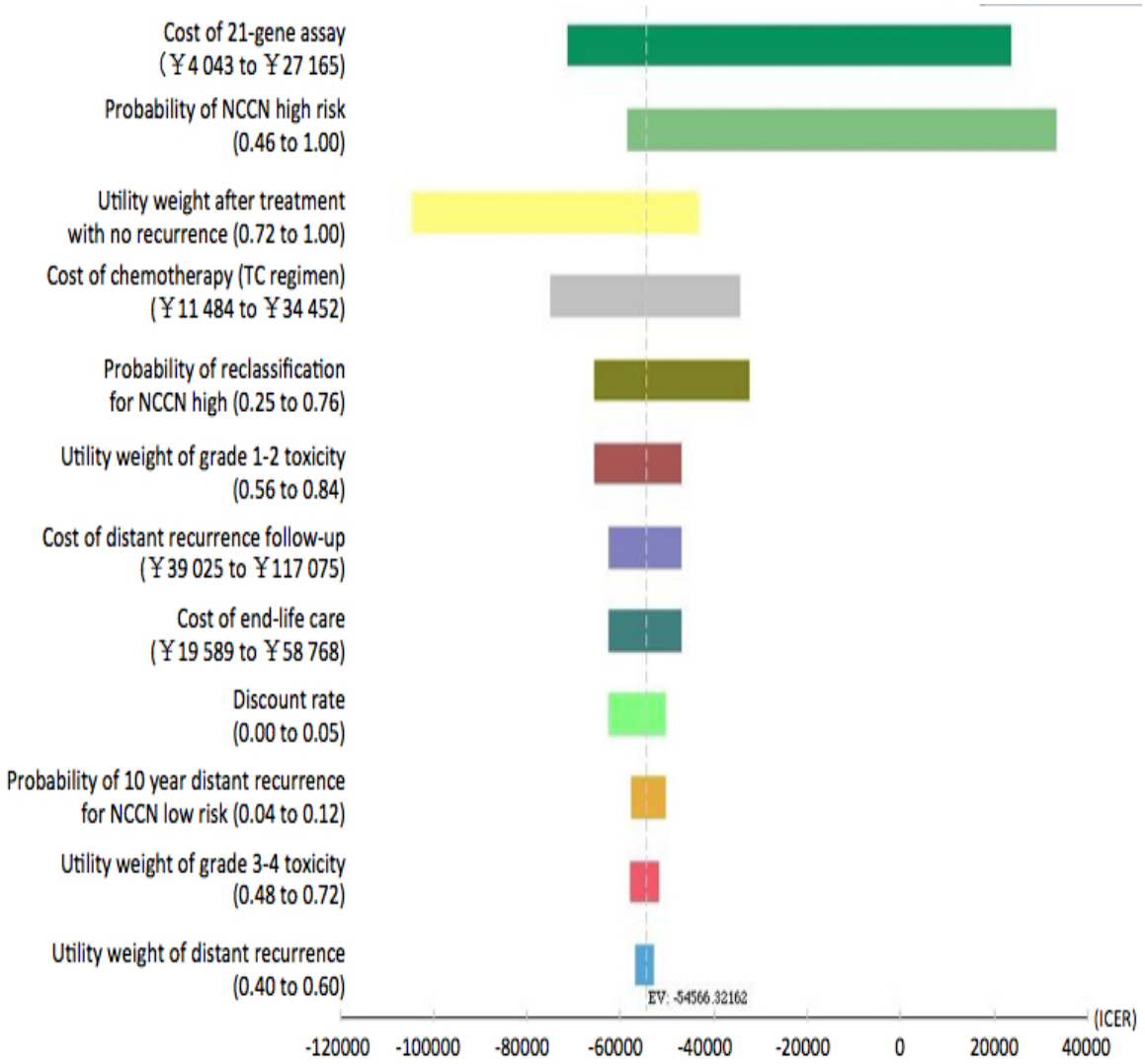

Figure 3.2 Results of sensitivity analysis with TC regimen

CHAPTER 4

DISCUSSION

The cost-effectiveness of 21-gene assay in the Chinese health care system was evaluated in this study for LN-, ER+, HER2-, ESBC patients. The results indicate, regardless of the chemotherapy regimen, compared to traditional guideline-based treatment, the diffusion of 21-gene assay gains more QALYs and saves money at the same time. Unless otherwise specified, the analysis in this chapter is based on base case analysis with AC regimen.

AC and TC are the two adjuvant chemotherapy regimens NCCN Guideline Chinese Version recommended for this patient cohort.[50] Under the base case analysis with AC regimen, 21-gene assay saves ￥11 125 (US$1 628) with a higher QALY of 0.30 year per patient over 10 years. Replacing the chemotherapy with TC regimen results in an even larger cost saving of ￥13 285 (US$ 1 934) but less effective gain of 0.24 year for treatment guided by 21-gene assay. This is due to the higher cost and lower recurrence rate of TC.[51] Studies have shown that in both the short term and long term, TC is associated with superior clinical outcomes to standard AC, regardless of patient age.[24,53] NCCN guideline 2012 version has removed AC from the recommended chemotherapy for HR+ patients.[16] Meanwhile, Liubao et al. indicated that compared with AC, TC is considered cost-effective in China with an acceptable ICER of ￥24 305

(US$3 556) per QALY.[51] It is expected that future updates to the Chinese Version of the NCCN Guidelines, will also replace AC with TC or another superior regimen. However, in our model the results are not sensitive to the cost and toxicity profile of the chemotherapy regimen. With either AC or TC as the adjuvant chemotherapy, NCCN-guided treatment is strictly dominated by the 21-gene assay-guided treatment.

The cost of 21-gene assay appears to be the major determinant of cost-effectiveness in our sensitivity analysis. Due to the unavailability of a retail price in China, the cost of the assay in the base case analysis is estimated as almost three times less than the U.S. price, based on the price differences among chemotherapy drugs between the two countries. Another price estimation strategy is setting the price compared to per capita GDP; according to the International Monetary Fund 2011, per capita GDP in China (US$8 382) is 5.7 times less than per capita GDP in the United States (US$48 387), which results in an even lower price for 21-gene assay.[72] A lower price of the 21-gene assay would contribute to an even larger cost savings for treatment guided by 21-gene assay. Even if the price is identical to the U.S. retail price as ￥27 165 ($3 975)[37], and the application of the assay become cost increasing, the ICER per QALY calculated as ￥26 551 (US$ 3 885) is still considered as cost-effective in terms of U.S. willingness-to-pay (US$50 000 or US$100 000 per QALY). Currently, China has no official guideline on the willingness-to-pay threshold. If China adopts the WHO's definition[73]: (1) highly cost-effective if ICER is less than GDP per capita; (2) cost-effective if ICER is between 1 and 3 times of GDP per capita; (3) not cost-effective if ICER is higher than 3 times GDP per capita, 21-gene assay-guided treatment would be considered as highly cost-effective with a price as high as the U.S. retail price.

Probability of risk classification by NCCN guideline becomes the second major factor in sensitivity analysis. The more accurate the NCCN risk classification becomes, the less cost-effective 21-gene assay becomes. In our sensitivity analysis, even if the NCCN guideline only recommends 46.05% patients to additional chemotherapy, the ICER of 21 572 ￥/QALY (3 156 US$/QALY) is still considered as highly cost-effective for 21-gene assay-guided treatment in terms of WHO thresholds. This situation is not likely to occur. Studies have shown NCCN guidelines tend to overestimate the recurrence risk and recommends adjuvant chemotherapy for most patients.[25] After all, 21-gene assay was specifically developed to solve the inaccurate risk classification problem of traditional guidelines.

Cost-effectiveness of 21-gene assay has been reported by 11 studies ever since the first validation clinical trial regarding this topic done in 2004.[32,37-46] They all demonstrated its superiority over traditional prognostic pathways of risk classification. Most studies demonstrated 21-gene assay would increase the cost and improve the quality of life with an acceptable ICER for 21-gene assay.[32,38-40,42,44-46] For example, Kondo et al. found an ICER of US$26 065 per QALY based on U.S. validation study in 2008 and an ICER of US$3 848 per QALY based on Japanese validation study in 2011, in the comparison between NCCN-guided treatment and assay-guided treatment.

A few studies considered treatment guided by 21-gene assay as a less expensive strategy.[37,39,41,43] Hornberger et al. found an acceptable ICER of US$31 452 per QALY for RS intermediate/high-risk patient and a cost saving for RS low-risk patient in 2005 and reported an average cost saving for US$1 160 per patient associated with 21-gene assay-guided treatment based on real-world cost reimbursement data in 2011. A study

conducted in Brazil, a developing country, found a cost saving of US$794 per patient on direct medical cost when applying 21-gene assay in 2010. Results of our study indicate a cost saving of US$1 628 per patient with AC regimen and US$1 934 per patient with TC regimen, which is consistent with the results of these studies.

Our study did not result in an increasing cost for 21-gene assay. This may be due to several reasons. First, a different perspective was utilized. Societal perspective is applied for most studies while health care provider perspective was adopted in this study which only accounts for the direct medical costs. Second, a lower price of 21-gene assay was used. According to our sensitivity analysis, cost of 21-gene assay is the major sensitive variable, and all of the 11 studies adopted a similar price to the U.S. retail price (around US$4 000), while our study made a cost estimation based on the cost difference on chemotherapy drugs and applied a much lower price (US$1 183), which may contribute to the different results. Third, different alternatives were used. For instance, in the study by Tosi et al., AOL, the alternative prognosis tool, only recommends 47% of the patients for chemotherapy. As we know from our sensitivity analysis, probability of risk classification by the alternative strategy is very sensitive to the results. Thus, a different alternative with a different power of risk classification in the comparison with 21-gene assay would influence the results.

4.1 Significance of This Work

As the most prevalent cancer among women, breast cancer is a significant burden of illness all over the world. The total cost of new breast cancer cases in Asia in 2009 is around US$1 928 million.[4] With increasing incidence rate and mortality rate,[47] the

economic burden of breast cancer in China will inevitably become an important question. Meanwhile, Chinese breast cancer patients are 17 years younger than in developing countries, with more aggressive disease and lower survival rates, which results in an enormous life-year loss.[55-58] Given the limited health care resources in China and the growing cost of the health care system, the economic evaluation of new health technology is warranted.

Our results indicate 21-gene assay contributes to a cost saving of ￥11 125 (US$1 628) per patient in China. For 190,000 breast cancer incidence cases in 2009,[47,49] this assay could save ￥105 million (US$15.5 million) for the country, if half of the patients would receive the assay. Meanwhile, better effectiveness is associated with the diffusion of 21-gene assay. We believe our model will help the decision makers in China make informed decisions to achieve better health outcomes and avoid unnecessary cost.

In China, the development of pharmacoeconomics is tardy, and the acknowledgement of the need for pharmacoeconomics is still inadequate.[74] However, in 2009, the Chinese government announced an official reform policy to providing universal access to healthcare services and formulating a national essential medicine system with government price guidelines.[75] In this reform, pharmacoeconomic evaluation was stated as the crucial criteria to form the essential medication list.[76] With the publication of draft Chinese pharmacoeconomics guidelines in 2006 and more and more cost-effectiveness studies in recent years, the awareness of the importance of pharmacoeconomics is developing in China. This study will contribute to that growing process.

4.2 Limitations

This study has some potential limitations. First, our model depends on the 21-gene assay validation studies performed in the U.S. Although evidence applied in the model are from the best available knowledge, the differences of characteristics between Chinese patients and U.S. patients might still lead to differences in clinical outcomes. We tested these differences by sensitivity analysis, varying the probabilities ±50% and the clinical outcomes (e.g., relative risk reduction, hazard ratio for TC compared with AC) in the 95% confidence interval range. And the results are robust to these changes.

Second, cost values in this study were from one local hospital. Generally, medication costs account for the majority of the total treatment costs, and within the same Chinese geographical area, the costs of most drugs should remain the same. Across regions, economic gaps do exist, especially between rural and urban areas. According to the statistics of the National Bureau, in 2009, the urban-rural income ratio was 3.33 to 1.[77] And these economic gaps will inevitably influence the drug prices. Our cost data source, the Second Xiangya Hospital of Central South University, is an upper-first-class hospital in Hunan province, a province with a midrange GDP per capita across the country, which makes this data source a rational base case for the sensitivity analysis to address the cost variation problem.

Third, utility weights adopted in this study were derived from Western reports. Usually, utility weights are different across countries, especially in Asian populations compared to Western populations. However, utility estimations for breast cancer patients are not available in China, nor in other Asian countries, and we can only

address this problem by generalizing the Western utilities on Chinese patients and vary the values by sensitivity analysis.

Fourth, toxicity profiles regarding the toxicity grade groups were derived from a clinical trial 22 years ago.[23] With the advance in care management and adverse event treatment, the clinical outcomes for toxicity have improved from that time. However, in the later studies, probabilities for a unique patient to experience toxicity during chemotherapy treatment are not available. Mamounas et al. found 0.3% of fatal toxicity for AC regimen in the study in 2005, comparing with paclitaxel plus AC.[78] Jones et al. stated no fatal toxicity during AC regimen and 0.3% of fatal toxicity during TC regimen. They also found around 10% of the patients would develop grade 3-4 neutropenia in either AC regimen or TC regimen.[24] With the risk of other grade 3-4 adverse events, such as infection, fever, and asthenia, we can expect higher probability of developing grade 3-4 toxicity for individual patients. These results are similar to the toxicity profile in our model .

4.3 Future Work

Future work includes expanding this study to lymph-node positive patients in China, since the prognostic value of 21-gene assay for these patients has been studied and reported by TransATAC and SWOG-8848 recently. Once benefit of chemotherapy for the intermediate-risk group being identified by the ongoing RxPONDER and TAILORx trial, further economic evaluation reflecting this change will become imperative.

To better understand the usefulness of 21-gene assay on Chinese patients, a Chinese validation study is needed for health managers to decide whether it fits in the clinical practice and health care system in China. In addition, further research should be undertaken to develop Chinese-specific quality of life instruments for use in the emerging pharmacoeconomics, in both urban and rural areas. Economic studies from a societal perspective with the life-year loss as the clinical outcome are needed. Also, studies regarding budget impact and the potential of covering by social insurance are warranted.

4.4 Conclusion

Twenty-one gene assay-guided treatment for lymph-node negative, ER positive, HER2 negative early stage breast cancer patients is considered cost saving and more effective compared with NCCN guideline-guided treatment from a Chinese health care system perspective. The results of this study should assist in making better clinical decisions for oncologists and patients as well as be interesting to health managers in considering expanding 21-gene assay use in China.

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