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Economic Dimensions of Personalized and Precision Medicine in Asia: Evidence from Breast Cancer Treatment in Taiwan

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Economic Dimensions of Personalized and Precision Medicine in Asia:

Evidence from Breast Cancer Treatment in Taiwan

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Abstract: High costs of precision medicine raise concerns about exacerbating income-related disparities in healthcare utilization and health outcomes. One approach to expanding coverage in Asia has been to cover the precision therapy but require the pharmaceutical firm to cover the costs of the companion diagnostic test. Taiwan's National Health Insurance (NHI) adopted this approach for lung cancer, colorectal cancer and leukemia, but not for the first target therapy covered by NHI, trastuzumab for the treatment of HER2-positive breast cancer. Analyzing a unique dataset linking medical claims, cancer registry data and proxies for income between 2004 and 2015, we find that lower-income patients are more likely to be diagnosed with later stages of breast cancer, and this pattern renders NHI coverage of anti-HER2 therapy pro-poor even before full coverage of the diagnostic tests.

Moreover, the expansion of NHI coverage—including the FISH diagnostic test and trastuzumab for early-stage breast cancer—strengthened the pro-poor distribution of genetic testing and target treatment, albeit only marginally. The extent of pharmaceutical company coverage of testing and its impact on patient access are topics of our ongoing research, contrasting breast cancer with colorectal cancer.

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The economic and clinical factors that affect the growth of personalized and precision medicine (PPM) have universal features, but also vary across countries and institutional contexts. The economies of East Asia are interesting cases for understanding how recent rapid economic growth and population aging interacts with changing technologies of care. Moreover, Asia provides an interesting institutional setting for understanding the economic dimensions of PPM coverage expansions and the role of contractual arrangements for paying for companion diagnostic tests. One approach to expanding coverage in Asia has been to cover the PPM therapy but require the pharmaceutical firm to cover the costs of the companion diagnostic test. Taiwan has embraced this approach for several cancers.

Such arrangements for protecting patients from the high costs associated with precision medicine treatment are important because otherwise the introduction and spread of PPM might exacerbate any existing income-related disparities in healthcare utilization and outcomes. Lack of knowledge and the costs of diagnostic testing and treatment are among the factors contributing to such disparities. However, to the extent that lower-income populations suffer disproportionately from an indication covered by precision medicine, such patients may also disproportionately benefit from the new technology and its diffusion in clinical practice. For example, if poorer patients with cancer tend to present with later stages of the disease, they may disproportionately benefit from precision medicine targeted to late-stage and/or metastatic cancer. We test this hypothesis for breast cancer as a case combining the two primary factors mentioned: propensity for poorest patients to be diagnosed at later stages, and among the first approved targeted

treatments.

This study is the first in a series that examines the Taiwan experience over the past decade with incorporating PPM into National Health Insurance (NHI) coverage, and its implications on disparities in treatment. Taiwan, as a prototypical "Asian tiger," has a system straining to finance universal health coverage under pressures of rising population expectations and the ever-increasing capabilities of medicine. The economics of Taiwan's coverage expansions present an interesting case, in part because Taiwan's NHI covers target therapies under agreement that the cost of genetic diagnostic testing for lung cancer, colorectal cancer and leukemia will be paid by the pharmaceutical firm supplying the treatment. However, the first target therapy NHI covered did not feature this contractual arrangement between NHI and pharmaceutical firms. NHI covered trastuzumab (Herceptin) for human epidermal growth factor receptor type 2 (HER2)-positive metastatic breast cancer without any agreement on who would pay for companion diagnostic tests. Although systematic data is not available, interviews and clinical experience suggest that prior to NHI coverage, genomic tumor testing costs for breast cancer were paid by the patient out-of-pocket, or occasionally by the provider's medical research fund on a case-by-case basis. The prevalence of pharmaceutical company coverage of testing and its impact on patient access are topics of our ongoing research.

Studies in many countries including the U.S. have shown the impact of coverage policies on disparities in breast cancer screening, stage at diagnosis, and treatment (e.g. Silva et al. 2017, Tarazi et al. 2017). For example, research on Medicare claims data by Layne et al. identified that 62.9% of

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breast cancer patients in U.S. territories (such as Guam and Puerto Rico) experienced a marked delay and poorer access to many standard treatments for breast cancer, as compared to their counterparts in the continental U.S., who are generally of higher income (Layne, et al., 2018). In China, Wang et al. (2012) found that 26% of women were diagnosed with stage III or IV breast cancer in low-SES regions, like Sichuan, compared to 15% in high-SES regions, like Beijing. Conversely, more women in high-SES regions were diagnosed with early stage breast cancer (28%), compared to 11% in low-SES regions. Women in rural areas tend to receive later diagnoses (stage > 3) than in urban areas. Chang et al. (2012) found a similar pattern in Taiwan, although there were issues with how they used the data to measure SES.

Our study focuses on breast cancer treatment as a case study in PPM expansion and whether PPM coverage is pro-poor or pro-rich in its utilization patterns. Breast cancer is a leading cause of cancer-related deaths worldwide among women. In 2012, there were 1.7 million new cases of female breast cancer globally, with an age-adjusted incidence rate of 47 per 100,000 women (WHO, 2012). In Asia, it is the second leading cause of cancer-related deaths among women, accounting for 39% of all breast cancers diagnosed worldwide (Fan, 2015). The incidence of breast cancer in Asia is 27 per 100,000, but varies widely across the continent. Moreover, the proportional contribution of Asia to global breast cancer has increased rapidly (WHO, 2012) and the mortality-to-incidence ratios have been higher in Asia than in Western countries, potentially because of lack of access to the latest effective treatments.

HER2 positivity accounts for almost one in five breast cancers, and a higher proportion—a little more than one in four breast cancers—among ethnically Chinese women (Li, et al., 2011). Target therapy has transformed treatment. As one recent clinical review noted, "anti-HER2 treatment…has changed the natural biology of this disease….and clearly improved the prognosis of HER2-positive breast cancer" (Loibl and Gianni, 2017), although it can be very expensive. Thus, providing access to anti-HER2 therapy is important for a Chinese population with growing incidence and prevalence of breast cancer, such as Taiwan.

The breast cancer incidence among females was 69.1 per 100,000 in 2013 in Taiwan, almost three-fold greater than the reported incidence in Asia, consistent with its higher income and rapid economic transition. Ethnically Chinese breast cancer patients present at an earlier age (cluster peak from 40-49 years old versus 60-69 years old) than U.S. women, and also with a higher prevalence of HER2-positive tumors (25.8% versus 15%) (Li, et al., 2011). As one of the only cases of PPM covered for many years by NHIA in Taiwan and other parts of developed Asia, the case of breast cancer treatment can elucidate how increasingly generous coverage of PPM, including coverage of the companion diagnostic test, can benefit lower-income patients. Policymakers clearly are concerned with controlling costs to assure access as well as improve quality, as manifested by a promising pilot program for bundled payment of breast cancer treatment (Wang, et al. 2017).[2]

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[2] We do not currently have access to information on which patients in our data may have participated in this bundled payment scheme since it is not crucial for the hypotheses tested in this study; we will include such data in follow-on research about

Using a unique, nationally representative dataset for breast cancer treatment and survival, we examine the roll-out and diffusion of this case of PPM, and analyze trends in disparities with a concentration index. The medical utilization for diagnostic tests and treatment therapies from NHI claims data can be linked to the cancer registry by using the individual's national ID created by the MOHW Health and Welfare Data Science Centre. We explore if there is income-related inequality in receiving genetic testing and target therapy for breast cancer under Taiwan NHI, and whether increasing coverage over time made the utilization more pro-poor. In Taiwan, pharmaceutical companies often cover the cost of diagnostic genomic testing, insulating poor patients from out of pocket expenses that might limit their access to testing and thus treatment. While no systematic data on the prevalence of firms' coverage of tumor testing is available for Taiwan, we can observe the extent to which cancer patients of different income levels accessed target therapy and thus deduce whether NHI coverage of testing made target therapy utilization more pro-poor.

To guide our hypotheses and interpretation, we utilize a simple model showing that the overall expected value of target therapy does not have an unambiguous monotonic relationship with SES. Poorer patients benefit more to the extent that they are more likely to be at later stage at diagnosis, but richer patients benefit more to the extent that they have higher willingness and ability to pay for target

resource use and supply-side incentives. According to the NHIA, only 4 hospitals participate in the breast cancer bundled payment scheme, two public hospitals and two foundation-owned hospitals. The breast cancer bundled payment scheme is mainly for inpatient services and there are quite a few "bundles" (i.e., different combinations of surgery, chemotherapy and other treatments). In general, if trastuzumab is given during the hospitalization, then it is covered in the bundled payment.

therapy, especially the combination target therapy of trastuzumab with pertuzumab that is never fully covered by NHI. Thus, *a priori* it is unclear whether the concentration index for trastuzumab-use will be positive or negative. We hypothesize that insurance coverage for this example of PPM may be pro-poor, given that coverage cannot erase disparities manifest in the form of poorer patients presenting at later stages of the disease, the stages for which target treatment was first developed and covered. We find empirical support for this conjecture.

The remainder of the paper is organized as follows. First, we provide background information on coverage of personalized medicine in Asia, an overview of Taiwan's health system, the epidemiology of breast cancer in Taiwan, and Taiwan NHI policies surrounding testing for HER2-positive breast cancer and its treatment. Then we articulate our hypotheses with a simple model, and introduce our data and empirical methods. The summary of results is followed by a brief discussion and conclusion.

Background

Coverage of personalized medicine in Asia

Study of approval and coverage of personalized medicine in Asia can contribute to the understanding of the trade-offs made in practice as such technologies diffuse in diverse parts of the world. Interviews we conducted in Taiwan as well as South Korea, China, and Japan, reveal that similar issues are salient to purchasers in East Asia as to purchasers elsewhere, including health

plans in the US: namely, efficacy and cost of the test, number of patients affected, and the extent to which the test results guide clinical treatment (Appold 2017; Pauly 2017). The coverage decisions for personalized therapies and their diagnostic tests usually proceed through the same steps of approval as for other tests, medications and devices. Following this logic, coverage for cancer tumor testing has generally been incorporated into standard insurance coverage in each country before coverage for other PPM, such as hereditary cancer predisposition testing (which to date is not covered in Japan, for example; Asano 2017). Trastuzumab (Herceptin) for breast cancer was among the very first precision therapies covered, starting in 2001 in Japan and 2002 in Taiwan (i.e., NHI covered trastuzumab treatment of metastatic breast cancer starting in 2002, prior to our study period). Indeed, in more recent years and for high-prevalence cancers, approvals occasionally occur in Asia first. For example, Gefitinib (Iressa, for lung cancer) was approved in Japan in 2002, prior to its approval in the U.S. and the EU (Asano 2017).

None of the East Asian countries studied explicitly incorporate cost-effectiveness into national insurance coverage decisions like NICE in the UK, but they all have a staged approval process that balances clinical benefits for patients with the realities of the budget process. Even in high-income Australia, the government created a separate "Herceptin Program" in 2001 to provide access for breast cancer patients because a cost-effectiveness analysis that year led to rejection of Herceptin for coverage (Neumann et al. 2017, p.12). The affordability of precision medicines is unsurprisingly a more stringent constraint for low- and middle-income countries, leading to large disparities in clinical areas most affected by PPM, like cancer diagnosis and treatment. Testing is sometimes

covered before treatment, given the high costs of the latter, as was the case in China for HER2-positive breast cancer before 2017. Although the testing had been covered by most insurance programs earlier, and Roche started a patient assistance program in 2011,[3] until recently only around half of breast cancer patients in China were tested and only about 30 percent of HER2+ patients actually use trastuzumab for treatment (Hicks, Liu, and Zhao, 2011). Trastuzumab was added to the insurance reimbursement list in July 2017 along with several other leading cancer drugs as part of a negotiated reduced-price agreement between pharmaceutical firms and China's Ministry of Human Resources and Social Security (Jourdan 2017).

There is also an interplay between coverage decisions and development of the biotech industry in the region. China launched a precision medicine initiative in 2016 with over US$9 billion in funding, and other countries in the region also aim to become global leaders in the field. More specifically regarding breast cancer treatments, for example, the first biosimilar to Herceptin, developed by Biocon and Mylan, received market authorization in India in 2013. The Korean Ministry of Food and Drug Safety approved coverage for biosimilar Herzuma in 2014, produced by the South Korean biotech company Celltrion; commercialization was delayed by a Roche patent infringement lawsuit, but Seoul Central District Court

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[3] "In collaboration with the Cancer Foundation in China and the Ministry of Health, we launched a patient assistance program (PAP) in August 2011 to address affordability. Under the program, after a patient has taken the first six cycles of Herceptin treatment, Roche donates the next eight cycles through the Cancer Foundation so that patients complete the full course of treatment."
http://www.roche.com/sustainability/what_we_do/for_patients/access_to_healthcare/making_innovation_accessible/ath_china_pap.htm

ruled in favor of the Korean firm in April 2017 (Sohn 2016 and 2017). Other firms in the region also aim to enter the breast cancer market; the Korean firm Alteogen, for example, is contracting with a Chinese firm, Qilu, in developing another Herceptin biosimilar.[4]

Similar to many other policy authorities in the region and globally, the Taiwan National Health Insurance Administration (NHIA) confronts some controversies in setting its reimbursement policy for precision medicines – to date, predominantly in oncology. At this point, Taiwan NHIA only reimburses a limited number of target therapies for cancer patients, for two primary reasons: first, these treatment regimens are high cost, generally without sufficient evidence (within an ethnically Chinese patient population) to prove effectiveness and cost-effectiveness. Second, institutional barriers limit scale-up because of questions about the validity and reliability of the diagnostic tests and the lack of TFDA-certified labs to conduct the tests. The Taiwan NHIA is looking for evidence to validate the effectiveness and cost-effectiveness of PPM diagnostic tests and treatment regimens.

Taiwan's health system

In 2015, Taiwan National Health Insurance (NHI) celebrated its 20th anniversary since its historic inauguration in 1995. The NHI program, which provides universal health coverage (UHC) to Taiwan's population of 23 million, has had a profound impact on Taiwan's health care market. The single-payer NHI program, operated by the National Health Insurance Administration (NHIA,

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[4] http://www.theinvestor.co.kr/view.php?ud=20170330000590, *The Investor*, March 30, 2017.

formerly known as Bureau of NHI), was established through integrating three existing social insurance schemes and extending coverage to the remaining 43% of the population who had been uninsured. Taiwan NHI offers comprehensive benefit coverage that includes ambulatory care as well as inpatient services. On the service side, Taiwan has a market-oriented health care delivery system, reflecting its free-enterprise economy, as evidenced by the pluralistic organization of health services. Hospital ownership is mixed, with public hospitals accounting for 35% of all beds. Sixty-three percent of allopathic physicians are salaried employees of hospitals; the remainder, fee-for-service private practitioners. Over the years, hospitals have developed large outpatient departments and affiliated clinics for primary care to maintain inpatient volume and compete with private practitioners who operate free-standing clinics with beds. There is no gate keeping mechanism and the insured essentially enjoy complete freedom of choice, which is likely a source of overuse (Lu, Hsiao, 2003; Lu, Chiang, 2011).

NHI revenue mainly relies on payroll-based premiums, supplemented by a levy on non-payroll income and government subsidies. In 2015, NHI spent roughly NTD 543.57 (USD 18.12) billion on medical claims, accounting for 52.81% of national health expenditures, and in total, Taiwan devoted 6.14% of GDP to health (Ministry of Health and Welfare, 2017). As a single payer, NHIA has effectively exploited its market power to experiment with various payment reforms in its 22-year history. NHIA gradually set up separate global budgets for dental services, Chinese medicines,

primary care services, and hospital services since 1998. The annual growth rate of the total NHI

budget is negotiated among stakeholders in the previous year.

Breast cancer and its treatment in Taiwan

In Taiwan, female breast cancer incidence has increased significantly over the past 30 years for all

age groups over 18. From 1980 to 2010, the mean incidence of breast cancer increased almost seven

times (from 11.40 to 73.27 per 100,000), with a 50% increase in the last decade. The 45-64 age group

experienced a threefold increase since 1981 (TCR, 2013).

According to the Taiwan Cancer Registry, incidence peaked at 164 per 100,000 among the 40-60 age

cohort, compared to Western countries where the peak incidence tends to occur among older cohorts

(age > 60) (TCR, 2013; DeSantis, 2016). This reflects a younger age of tumor onset (Shen, 2005). More

than 50% of patients diagnosed with breast cancers in Asian countries are premenopausal, a proportion

nearly twice that of Western countries. Similarly, the incidence ratio between younger (age < 50) and

older patients (age > 50) with breast cancer is 0.55, which is also double that of Western countries (0.26)

(Parkins, 1993; Huang, 2010).

In 2010, the breast cancer age-standardized mortality rate in Taiwan was 18.1 per 100,000. Breast

cancer mortality rates have increased more than twofold from 1971 to 2010. There was a 55% increase

in mortality for the 20-44 age group, and a 150% increase for the 45-64 age group (Ho, 2015), at the

same time that mortality was decreasing in western countries. The 1-year survival rate for all breast

cancer stages in females was 97.3%, and the 5-year survival rate was 83%, which is comparable to 5-year survival in the U.S. and Europe (TCR, 2013).

With NHI providing 99% coverage since 2004, cancer care is almost universally accessible to patients in Taiwan. Biennial breast cancer screening and mammography have been available without charge to patients as well. Pan et al. (2014) found that in 2011 and 2012, the biennial mammography coverage rate was 33.2%. Increasing resources have been devoted to screening, including adoption of digital mammography, mobile mammography units, and the certification of radiologists and radiographers. As these resources grow, the coverage rate is expected to grow as well (Pan, 2014). The age 40-49 cohort had the highest rate of mammography, breast ultrasound, and physician examination, corresponding with the recommended age for Asian women to begin breast cancer screening (Lin, 2008; Tsuchida, 2015). Despite the increase in screening utilization over the past decade, disparities still exist. For example, high school graduates were half as likely to receive a mammogram or breast ultrasound as college graduates (Lin, 2008). In addition to disparities in knowledge, awareness, and prevention, those living in more remote areas of the island might also face geographic constraints in accessing treatment. As Einav et al. (2016) highlight, even in the US and other high-income countries, distance to the nearest provider for repeated treatments such as radiation therapy can significantly shape treatment decisions.

NHIA requires gene testing for all cancer target therapy. During our study period, the only gene expression tests for target therapy that were covered by NHI were IHC since 2004 and the fluorescence in-situ hybridization (FISH) since 2009. Breast cancer target therapy will only be

covered if IHC tested 3+ or FISH tested positive (Figure 1); the FISH test might be performed if the

IHC test was suggestive but not definitive, such as 2+. In contrast, as noted above, for other cancers

including lung cancer, colon cancer and leukemia, companion diagnostic tests are generally paid for

by the pharmaceutical firm supplying the treatment, sometimes supplemented by the patient's

own out-of-pocket payments or by the provider's medical research fund.

In our empirical analyses, we examine whether the cost of genetic testing potentially could be

an access barrier to target therapy for breast cancer patients by utilizing the natural experiment of

2009 coverage of the FISH test, as well as the 2010 coverage of trastuzumab treatment for early-

stage breast cancer.

Our study is constrained by the fact that there will be no data in NHI claims if the testing or

treatment is not covered by NHI. Accordingly, we are likely to underestimate actual utilization of

target therapy among the highest-income patients, who are those most likely to pay for such

treatment out of their pockets. Even though NHI covered trastuzumab, pertuzumab is not covered

by NHI, so we have no data about whether higher-income patients were more likely to utilize the

combination target therapy of the two (a likely case, given that the latter adds additional treatment

efficacy). In addition, per NHI guidelines, one needs a positive testing result before target therapy

treatment can be covered; however, we do not observe the test results, only the prescription of the

test. So we are testing whether the probability of targeted treatment will less significantly differ

with income quintile after NHI expands coverage—first, for FISH testing, then for early-stage cancer

(i.e., if utilization will be more pro-poor than it was before the coverage of the test). NHI coverage for both the companion diagnostic and the treatment may erase income-related inequalities (disparities) in utilization of targeted therapy for a given stage of cancer, and disproportionately benefit poorer patients who present with the later stage cancer. The next section presents our hypotheses with greater precision, using a simple model.

Conceptual framework

Let h represent the probability that an individual with breast cancer has the HER2-positive molecular sub-type of breast cancer and thus would benefit from anti-HER2 target therapy. We study this case in part because we know h is relatively large for ethnically Chinese women (25.8% prevalence of HER2-positive tumors, compared to 15% in the general US population; Li et al., 2011). We assume that all Taiwanese have the same basic genetic propensity and therefore that h is constant, independent of income y or broader measures of socioeconomic status (SES). The expected value of target therapy, EV, depends on the individual's clinical appropriateness, as well as willingness and ability to pay for the treatment, given NHI coverage policies. For example, prior to 2009, coverage was conditional on having metastatic HER2-positive breast cancer. In other words, any woman with early stage cancer, or late stage cancer that was not yet metastatic, could not have trastuzumab covered by NHI and instead had to pay for the treatment themselves. Let $\omega(y)$ represent the stage of breast cancer at diagnosis. Unlike h, we hypothesize this probability will be a

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function of income, because the likelihood that breast cancer is detected at an early stage is likely to be increasing with income: $\omega'(y) < 0$. We see this tendency for higher-SES patients to receive diagnosis and treatment at earlier stages of cancer in many parts of the world.[5]

Hypothesis #1: The likelihood that a given patient will have more advanced (later stage) breast cancer at diagnosis is decreasing in income: $\omega'(y) < 0$.

Let $V(m; y, \theta)$ represent patient utility from treatment, where *m* represents spending (resource use) for target therapy, and θ is the patient co-insurance rate for services covered by insurance ($0 \leq \theta < 1$, equal to 0 when fully covered by NHI).

The expected value of NHI-coverage for target therapy depends on the probability of a patient having HER2-positive breast cancer, the stage at diagnosis, and the demand for target therapy given NIH coverage policies:

$$EV(m) = h\,\omega(y)V(m; y, \theta)$$

Although the rich and poor are equally likely to be HER2-positive, they do not enjoy the same EV. The overall expected value of target therapy does not have an unambiguous monotonic

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[5] In addition to the sources cited in the introduction, see for example Daly and Olopade (2015) and sources cited therein highlighting that in the US, African American women present at more advanced stages of breast cancer. As noted, in Taiwan, high school graduates were half as likely to receive a mammogram or breast ultrasound as college graduates (Lin, 2008). Similarly, in Hong Kong, Chan et al. (2002) found women with lower education were less likely to receive a clinical breast examination or to perform a breast self-examination, compared to women with higher educational attainment.

relationship with SES. On the one hand, poorer patients benefit more from NHI coverage of trastuzumab to the extent that they are more likely to be at a later stage at diagnosis; especially prior to 2010, poorer patients would be expected to benefit from trastuzumab coverage if, as hypothesis #1 surmises, they are more likely to be metastatic at diagnosis (M1) or to develop metastasis during the study period (i.e., because they are at a later stage at initial diagnosis). In other words, the first term $h \, \omega(y)$ is higher for low-income patients. However, the second term $V(m; y, \theta)$ is higher for richer patients to the extent that they have higher willingness and ability to pay for target therapy, especially the combination target therapy that is never fully covered by NHI. Thus, *a priori* it is unclear whether the concentration index for trastuzumab-use will be positive or negative; it is an empirical question we address in this study.

Hypothesis #2: The overall association between patient income and receipt of trastuzumab may be positive or negative; the greater the propensity for low-income patients to present with later stage disease, the more likely that target therapy utilization is pro-poor (i.e., with a negative concentration index), especially prior to the 2010 extension of coverage to patients with early-stage breast cancer.

NHI coverage of trastuzumab and the IHC companion diagnostic test—but not of complementary target therapy such as pertuzumab (or before 2009, the FISH companion diagnostic test)—can be considered a kind of "top-up" insurance policy, with potential efficiency properties, depending on ex ante risk (Einav, Finkelstein, and Williams 2016). Taiwan's coverage before 2009

was equivalent to a deductible for the FISH diagnostic test, and then $\theta = 0$ if the patient had HER2-positive metastatic breast cancer and did not also use pertuzumab. In 2009, this deductible was removed (the FISH test was fully covered) for metastatic cases.

Hypothesis #3: The proportion of lower-income patients receiving target therapy increases after 2009 when the more expensive of the companion diagnostic tests, the FISH test, is covered by insurance.

Following on the heels of the FISH policy change, in 2010 the NHI removed the requirement of having metastatic cancer in order to qualify for trastuzumab treatment. In other words, trastuzumab was reimbursed for patients with early-stage breast cancer starting in 2010. The requirement to self-pay for pertuzumab therapy—i.e. a substantial co-insurance requirement ($\theta > 0$) for combined trastuzumab+pertuzumab target therapy[6]—continued throughout our study period, so higher-income patients might be more likely to be able to "top-up" to full coverage for the most effective target therapy combination for HER2-positive breast cancer. Unfortunately, with the NHI data in this study, we cannot observe the use of any services not covered by NHI; thus, we do not know which patients received the combined target therapy by paying out-of-pocket for pertuzumab. However, we do observe survival, which may provide some insight into which patients had access to the combined target therapy that extends survival.

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[6] A course of pertuzumab treatment could cost over $60,000 USD.

Data and empirical methods

Data description

The data files linked to construct the study sample include the cancer registry, death registry and NHI claim files (including both inpatient and outpatient services). Recognizing the rising trend in cancer incidence, the Taiwan Department of Health (DOH, now Ministry of Health and Welfare, MOHW) launched the Taiwan Cancer Registry (TCR) in 1979 to monitor cancer incidence. Since then, the TCR central office has collected basic information (short-form database, 20 items, now 42 items) on newly diagnosed malignant cancer patients from hospitals with more than 50 beds throughout Taiwan. Starting in 2002, the scope of data expanded to include more detailed information such as cancer staging, first course of treatment and follow-up data (long-form database, 65 items, now 114 items). With the enactment of the Cancer Control Act in 2003, DOH made the reporting process mandatory for all medical institutions and launched a trace-back procedure to enhance the quality of the cancer registry. To date, the long-form database accounts for more than 90% of total cancer cases in Taiwan (Chiang et al., 2015). The quality of the cancer registry has been validated by indicators such as morphologically verified cases (MV%), the mortality vs. incidence ratio (M/I%) and the percentage of death-certificate-only cases from 1980-84 to 2000-06; each of these measures has shown steady improvement (Chiang, 2010). Breast cancer is one of the six cancers with mandatory reporting since 2004; our analytical sample is hence restricted to newly diagnosed breast cancer

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cases identified in 2004 and later. While we cannot rule out differential coverage by income or other socioeconomic factors, the 90% coverage rate of the cancer registry by 2015 provides some reassurance.

Taiwan implemented its NHI program in 1995 and has released the claims data and registration files for research use via the National Health Research Institutes (NHRI) since 2000. In the face of rising public concern over patient confidentiality, since 2015 MOHW has restricted access to NHI claims data to the Health and Welfare Data Science Centers, one of which we used for this study. We linked the cancer registry data to NHI claims data that includes all insurance-covered utilization, including prescription and other medications, outpatient and inpatient services, and the characteristics of the provider (e.g. physician specialty, clinic or hospital and its ownership). To examine whether patterns of use differ by geographic region, we code each patient to one of six NHI division offices, as well as utilize an official designation of geographically remote areas (based by the MOHW definition). To obtain information on monthly insured wage and residency proxy, we have also used the registry of beneficiaries (underwriting) file.

Figure 2 depicts the sample construction process. We identified newly diagnosed breast cancer patients (ICD-O-3 beginning with C50.XX) from the 2004-2013 TCR long-form database (N=86,618) and then linked those records with 2004-2015 NHI claims data, as well as the registry of beneficiaries and death registry. The claims data provides information on treatment and

medication as well as some SES variables (location of NHI enrollment and, for some enrollees, insured monthly wage), to be discussed in more detail below.

Cancer staging is crucial for our analyses, but we discovered that there are a non-trivial number of missing values for staging in the cancer registry data. Breast cancer is staged using the American Joint Committee on Cancer (AJCC) TNM system, which is based on 3 key pieces of information: the size of the original tumor (T) and if it has grown into nearby areas; whether the cancer has reached nearby lymph nodes (N); and whether the cancer has metastasized (spread to other parts of the body) (M). The M staging variable is missing for 6.8% of our analytical sample. The TCR also codes the overall stage (Health Promotion Administration, 2016).

To link up the data from the TCR, NHI claims and registration, and death registry, all the analyses were conducted at the Health and Welfare Data Science Center at Chang Gung University branch site. We obtained IRB approval for this study from the Research Ethics Office of National Taiwan University.

Despite the comprehensive information regarding utilization embedded in the NHI database, a drawback is its lack of socio-economic information, such as educational attainment, household income and residency (the NHI data also do not include any information about the testing results or any services that were paid for entirely out-of-pocket).

To study whether coverage mitigated disparities in utilization, we developed two strategies to measure the economic status of breast cancer patients.   One is to use the monthly insured wage in the Registry of Beneficiaries file. While this data is appealing because it is accurate at the individual level, it is only available for a specific sub-group of the population ("Category I insured"), namely, people who are also insured by Labor Insurance (workers in the formal sector) and Government Employee Insurance (government employees and faculty members in private schools and universities) (Lien, 2011). As the lowest monthly insured wage is the legal minimum wage, we have deleted observations with reported insured wage less than the minimum wage. Our second method is to use the district-specific median household income for all 368 districts from the tax return data released by the Ministry of Finance. We used median income data for year 2012, as it was the first year when the teachers in elementary, middle and high schools and military service personnel were required to file tax returns. Contingent upon the income proxy we used, we have two analytical samples: for the full sample of patients, we use the district-specific median household income (from tax returns); and for the formal sector and government employees (hereafter, the GEI/LI sample), we use the reported monthly insured wage in the NHI Registry of Beneficiaries.

To examine potential disparities by geography, we also coded residency location for each patient. NHI records the location of NHI enrollment, which is where the office of the employer is situated but not necessarily the residential location of the insured, particularly for those who work for large corporations. For example, big companies tend to set up headquarters in the capital city, Taipei, but

many employees work at a factory or office outside the city (in a suburban or rural area) and reside near there. We hence adopted an algorithm to determine the residential location of a breast cancer patient based on her occupation (which corresponds with insured category) and where she utilizes primary care services (Figure 3) (Lin, Yang, Wen, 2011).   Then the residency location is matched with district-specific median household income to obtain the economic status proxy for our study sample.

Empirical methods

As one measure of income-related inequality in health care use (in this case, either diagnostic testing or target therapy), we computed a concentration index (*CI*), with estimates for *CI* and its robust standard error obtained by running the following convenient regression (Kakwani, Wagstaff, van Doorslaer, 1997):

$$\frac{2\sigma_R^2}{\bar{y}} y_i = \alpha + \beta R_i + \varepsilon_i \qquad (1)$$

where *y* is an indicator variable for whether the patient obtained the test or used target therapy (0,1), $\bar{y}$ is its mean, R_i is the relative fractional rank of the *i*th individual in the income distribution and σ_R^2 is the variance of R_i. The ordinary least squares (OLS) estimate of the slope coefficient (β) is the estimate of *CI*.

When studying changes in utilization associated with the 2009 coverage of companion diagnostic testing with FISH (a specific test for breast cancer patients with suggestive, but not definitive, IHC

testing results, such as 2+), it is most relevant to limit analysis to patients with metastatic disease at diagnosis (M1), the relevant group for comparing access before and after that policy change. However, given the limited sample size, concerns regarding missing data for M1, and the possibility of developing metastases after initial treatment, or case-by-case consideration of NHI coverage even for non-M1 cases, it is also instructive to compute $CI_{TW,t}$ at the national level for the entire sample for each year (t=2002-2015) to see whether there is a trend across the years, and any jumps associated with the policy changes (i.e., FISH test coverage in 2009 and the extension of trastuzumab coverage to early-stage cancer in 2010).

We also estimated logit regressions to test for disparities in diagnostic testing and target therapy utilization by income quintile, and its change after FISH testing was covered. The patient is categorized according to the year of diagnosis, recognizing that they continue treatment into subsequent years. We report the marginal effects from a logit regression to assess the association of utilization with income (Norton and Dowd, 2017). Finally, as a preliminary examination of the correlates of patients' outcomes, we estimated Kaplan-Meier all-cause 5-year survival curves by income quintile and by metastasis, adjusted for age and Charlson comorbidity index at diagnosis. Full examination of disparities in outcomes, accounting for censoring in our data, is left to future research.

Results

In our analytic sample of breast cancer patients in Taiwan, the year of diagnosis ranges from 2004 to 2013. Roughly 62% (70% for the GEI/LI sample; see Table 1) of breast cancer patients were diagnosed between the ages of 40 to 59; the mean age at diagnosis was 53.46 years old (50.24 for the GEI/LI sample). Approximately 40% of the patients resided in the Taipei area (i.e., within the jurisdiction of the NHIA Taipei division office); within the sample of patients employed and insured under GEI or LI, there was a slightly higher concentration in the Taipei area (44.64%). The distribution of patients by tumor stage at diagnosis is 11.89% (13.52% for the GEI/LI sample) with tumor localized/in situ (Stage 0); the majority are diagnosed at an intermediate stage, and 2.84% (2.14% for GEI/LI sample) have metastatic breast cancer already at diagnosis (M1). The M staging variable is missing value for 6.48-6.8% of the sample. As shown in Table 1, average years survived is 5.57 years (5.69 years for GEI/LI sample), distributed from 0 to 11.99 years (survival is truncated at 12/2015). Among those in our sample, the year of death ranges from 2004 to 2015; 16.51% of the sample patients (11.94% for GEI/LI sample) died during the observation period (Table 1). The Charlson Comorbidity Index score varies from 0 to 20; approximately 37.04% have a score of 2 and roughly 21.32% have a score of 8 (43.36% and 22.74% for GEI/LI sample, respectively) (Table 2).

Hypothesis #1 garners clear support in our data, suggesting that trastuzumab coverage may be pro-poor. In Figure 4, we show the proportion of patients who are late stage versus early stage by income quintile. For both samples and measures of income, there is a gradient with lower income patients being more likely to be diagnosed with later stage cancer. For example, as hypothesized and consistent

with earlier literature, the probability of metastasis at diagnosis is higher for those with lower income (Figure 4A and Table 4 last column). In the full sample, 20.8% of women in the lowest income quintile are Stage III or IV, compared to 16.4% among those in the highest income quintile (Figure 4B); similar patterns arise in the GEI/LI sample, with a 4.7 percentage points difference in late-stage (Stage III or IV) cancer between those in the lowest and highest income quintiles (Figure 4C). Focusing only on those without metastasis, Figure 5A shows that in the full sample, 17.6% of women in the lowest quintile of income are diagnosed as stage III, compared to 13.9% of women in the highest income quintile. Among the GEI/LI sample, that difference is 15.8% compared to 11.9% (Figure 5B).

We observe that about 79.35% (81.01% for GEI/LI sample) of sample patients had an IHC test (a general, low-cost test), 11.44% (11.88% for GEI/LI sample) had the FISH test, and roughly 10.82% (10.16% for GEI/LI sample) received target therapy with trastuzumab (Table 3A, 3B). Regarding testing, it is important to note that in up to 25% of cases, HER2 status may be discordant between the primary tumor and metastases, leading some to recommend (re-)testing of both primary tumor and the metastatic lesion at relapse (Loibl and Gianni, 2017). Among patients receiving trastuzumab, most were treated at foundation-owned (private not-for-profit) hospitals, followed by public hospitals. Regarding the specialty of the primary provider, for both full and GEI/LI samples, roughly 82%/65%) (83%/65.5% for the GEI/LI sample) of the sample patients had IHC/FISH testing managed by a surgeon, compared to 3%/21% (2%/20.6% for the GEI/LI sample) by an oncologist. However, approximately 47% of the sample

patients had trastuzumab prescribed by an oncologist, and 42% by a surgeon (46% and 42.8%, respectively, for the GEI/LI sample) (Table 3A, 3B).

We tested our primary hypotheses by estimating a concentration index for different samples of patients and different years. In addition to the full sample and GEI/LI sample of all-stage cancer patients, we also examined the income-related inequality in the use of IHC and FISH tests and trastuzumab for the M1 metastatic sample (who would not be affected by the extension of indication to M0 patients since 2010).   As shown by the CIs in Table 4, the use of IHC companion diagnostic testing shows a pro-rich distribution and the utilization of FISH companion diagnostic testing tends to be proportionally distributed. A pro-poor inequality in the use of trastuzumab is observed, although the magnitude appears to be modest.   Overall, the significance and magnitude of the inequality are more obvious in the full sample than the GEI/LI sample, i.e., those for whom we have the more accurate income proxy based on monthly wage. Confirming the summary statistics shown in Figure 4, metastasis at initial diagnosis (last column in Table 4) exhibits a marginally pro-poor distribution of most advanced (i.e., already metastatic) breast cancer.

Further, we aggregate the observations into pre- and post-policy periods to examine patterns of use before and after the expansion of coverage, by M status (Table 5). We define the pre-policy period (labeled "pre-period[1]") as 2002-2008 to represent the period before FISH was covered by NHIA, except in the case of the non-metastatic sample, where the pre-period is 2002-2009 (before the extension of indication to cover M0 patients). Accordingly, the post period is 2009-2015 for the "all" sample and M1

sample (after FISH is covered by NHI); but 2010-2015 for the M0 sample (after the extension of indication to cover M0 patients). Aside from the definition above (pre-period[1]), to try to disentangle the effect of the coverage expansions from the natural course of the disease (e.g. M0 patients developing metastases in the pre-2010 period and gaining access to trastuzumab), we also deleted patients diagnosed in the pre-policy years but who received testing or trastuzumab in the post-policy period (labeled pre-period[2]).

All the CIs that are statistically significant both for the full sample and for the GEI/LI sample in any of the periods are negative, showing the distribution of the use of trastuzumab is pro-poor (Table 5). The overall CI for the full sample is -0.0124, a modest magnitude. The magnitude of the post period CI is slightly larger than the pre-period CI, suggesting that the expanded coverage strengthened access for the poor. Comparing the two definitions of the pre-period, we see that pre-period[1] estimated CI is more pro-poor than that of pre-period[2] which excludes those who gained delayed access to trastuzumab in the post period. This difference implies that more poor patients gained delayed access than rich patients did, both in the full sample and the GEI/LI sample. The pro-poor tendency in the all-stage cancer sample (M0+M1) mainly comes from the much larger sample of M0 patients, where the CI for pre-period[1] (which includes those with delayed access) is significantly more pro-poor than the CI for pre-period[2]. For those with non-missing codes for M and metastatic cancer at diagnosis (i.e., the M1 sample), the CI are only marginally statistically significant (albeit of larger magnitude than for M0), although several estimates are indistinguishable from zero.

As a robustness check to the CI analyses, we also examined the likelihood of receiving target

therapy by income quintile, controlling for age at diagnosis and co-morbidities. These descriptive

regressions (Tables 6 and 7) confirm that the policy of better insurance coverage (for the FISH

diagnostic test as well as for earlier stages of breast cancer) is associated with a statistically

significant increase in trastuzumab use. The post policy estimated coefficient is significant for

almost all samples. The highest-income non-metastatic patients were less likely to receive

trastuzumab in the pre-period (Table 6), consistent with their greater likelihood of having the

earliest stage of cancer. The interaction of post and income is not significant, although the region of

residence indicator variables (which are also correlated with SES) are jointly significant. Among

metastatic cancer cases, trastuzumab treatment is unrelated to regional median income, although

there is some evidence that those with both the lowest and highest insured wage quintiles received

more NHI-covered target therapy in the post period (see Table 7). We find slightly stronger results

when excluding patients who were diagnosed prior to the policy change but who received the FISH

test after the policy change. There is only weak support for hypothesis #3, that the proportion of

lower-income patients receiving target therapy increases after the FISH test is covered by insurance.

This might be expected: only a small proportion of patients will fall in the intermediate zone where

an IHC is ambiguous but a FISH test would be definitive, and it is difficult to tease out exactly which

patients benefited since (a) we do not observe test results and (b) the FISH test coverage happened

so close to the 2010 policy change affecting a much larger proportion of patients.

Thus, overall we find that among women diagnosed with M0 breast cancer before 2010, trastuzumab use was higher among low-income than high-income women (the CI is negative, and the regression shows patients in the highest income quintile were less likely to receive trastuzumab). This is consistent with poorer women being diagnosed at later stages and more likely to develop metastases (e.g. in our data 70 patients diagnosed M0 in 2005 were prescribed trastuzumab in 2007). When examining the differences between M0 patients who receive trastuzumab before and after 2010, we find the pre-2010 users were more likely stage III and far more likely to die during our study period, as would be the case for those women who developed metastatic cancer. Of course the differential could also be because high-income women are more likely self-paying for target treatment not covered by NHI (which we cannot directly observe in this data), or other reasons.

An examination of survival differences—accounting for censoring, differential "missingness" of staging and other factors—is left for future research. However, it is worth noting that we do observe the highest income patients enjoying longer survival, as shown in Figure 6A (full sample) and 6B (GEI/LI sample). Unsurprisingly, the primary differentiator for survival is cancer staging, with metastatic cancer associated with significantly lower survival (Figure 6C). The survival curve for those with missing data on metastasis lies in between the curves for metastatic and non-metastatic cases; this pattern suggests that some of those with missing meta status did indeed have metastatic breast cancer. A corollary of our simple model and hypotheses would be that, conditional on stage of cancer at diagnosis, both before and after the coverage expansions, the proportion receiving combined target therapy by paying

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out-of-pocket for pertuzumab increases with income, resulting in longer survival for higher-income patients. Both earlier stage at diagnosis and access to self-paid combination therapies may contribute to the observed longer survival of those with higher income, evident at 3 to 5 years for the GEI/LI sample (Figure 6B). That access to combination therapy probably plays a role in this survival differential is suggested by the fact that, conditional on stage at diagnosis, the likelihood of receiving trastuzumab differs only slightly across income quintiles (Figure 7).

Discussion and conclusion

We examine the case of breast cancer treatment in Taiwan to exemplify the potential of PPM to be pro-poor, with coverage extensions further expanding access to PPM treatment and reducing disparities. Although not all health systems can afford such comprehensive coverage as Taiwan's NHI provides for breast cancer patients, and we have not assessed the overall welfare impact including the opportunity costs of the associated expenditure increases, Taiwan's experience illustrates that PPM coverage can disproportionately benefit the poor, even when introduced without full coverage of the companion diagnostic tests.

Specifically, we hypothesized that the overall association between patient income and receipt of trastuzumab therapy may be positive or negative, and the greater the propensity for low-SES patients to present with later stage disease, the more likely that target therapy utilization is pro-poor (i.e., with a

negative concentration index). The data show that lower income patients are indeed more likely to present with later stage disease (more advanced stages of breast cancer) in Taiwan. For the most advanced stage, the distribution of metastatic cases is marginally pro-poor for both proxies for income, although the magnitude is modest.

Perhaps more importantly, we find that the inequality in use of trastuzumab treatment, as measured by the CIs among patients with all stages of cancer, are pro-poor, statistically significant, and are larger in magnitude in the post-policy period than the pre-policy period (Table 5). These patterns are consistent between the full sample and the sample of employed formal sector workers with a more accurate individual-level income proxy (GEI/LI sample). Hence, it seems that the fact that lower-SES patients are more likely to be diagnosed with later stages of cancer outweighs the presumed access advantage possessed by the rich, rendering NHI coverage of target therapy pro-poor even before coverage of the diagnostic test. Moreover, those who gained "delayed access" by the expansion of NHI coverage—including the FISH diagnostic test and of target therapy for earlier stages of breast cancer— were disproportionately poor, strengthening the pro-poor distribution of target treatment.

The lack of a significant impact of NHI coverage of FISH tests for pro-poor access suggests that the costs of testing did not significantly deter low-income patients from treatment, either because the testing costs are small relative to those of therapy or because the testing costs were covered by others in ways we cannot observe in our data prior to NHI coverage, such as coverage by pharmaceutical companies or provider research and access funds.

When looking at genetic testing in our data, we found that the use of IHC, which is a low-cost genetic test that is not specific to breast cancer, shows a pro-rich inequality in use, whereas no income - related inequality is found among users of the FISH test. This may imply that the well-off have better awareness and access to general genetic testing, although access to the more specialized and expensive test (which we only observe after it is covered by NHI) is not disproportionately used by those with higher income. In ongoing research, we are studying the prevalence and possible impact of pharmaceutical companies' coverage of companion diagnostic testing in Taiwan and other parts of East Asia.

To assist with putting these results in policy perspective, we develop a back-of-the-envelope estimate of the total life-years saved by the NHI expanded coverage policies for both metastatic and early stage breast cancer patients. We estimate that for women diagnosed with breast cancer in the 4-year period 2010-2013, NHI trastuzumab coverage policy led to an additional 6,600 to 33,200 life-years, depending on the range of the estimates of life-years saved by trastuzumab treatment for early stage (from 1 to 5 years) and metastatic breast cancer (0.25 to 1.2 years), with a preferred estimate of about 20,000 life-years.[7]

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[7] For patients with metastastic breast cancer, we estimate trastuzumab extends survival by 3 months, but with a range of up to 14 months for those who also self-pay for pertuzumab (Danese et al. 2015). Estimates of life-years saved for patients with early-stage breast cancer come from the literature (see for example Romond et al. 2005; Slamon et al. 2011; Perez et al. 2014), with the preferred estimate from Garrison et al. (2007), who projected life expectancy was 3 years longer for patients who received trastuzumab (19.4 years vs 16.4 years).

The data does not include those who self-pay for testing and target therapy, which almost surely means we underestimate disparities in use, because we do not observe the number of (presumably higher-income) individuals paying entirely out of pocket for testing and target therapy in the early years before the treatment became standard of care for HER2-positive breast cancer.[8] In future research, we will examine the data available in the Taiwan cancer registry starting in 2011 which records whether a patient received target therapy (even if such therapy was not covered by NHI). If that data is coded with reasonable completeness, it will enable us to observe the distribution of target therapy for those who have breast cancer but who are not receiving treatment covered by NHI. We also will examine patient records for a large provider that includes data on all treatments received, including both NHI-covered services (e.g. trastuzumab) and self-paid services (e.g. pertuzumab).

Future research will also explore potential interactions with supply-side incentives based on fee-for-service or bundled payment (Wang, et al. 2017), specialty of provider, level of accreditation and ownership of the clinic or hospital. Finally, an extension will contrast the case of breast cancer with that

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[8] The disparities we estimate represent an underestimate of gaps in utilization in the pre-policy period to the extent that we are missing a population of high-income patients who are able to receive therapy by paying out-of-pocket for such treatment. This under-estimation would be mitigated, and the estimated disparities could even represent an over-estimate of the gap between rich and poor, if in the post-policy period rich patients continue to receive target therapy by paying out-of-pocket rather than availing themselves of NHI coverage. Our estimates nevertheless are an accurate estimate of disparities in NHI-covered utilization and its targeting being pro-poor.

of colorectal cancer, where pharmaceutical firms pay for the companion diagnostic tests in exchange for

NHI coverage of their target therapy.
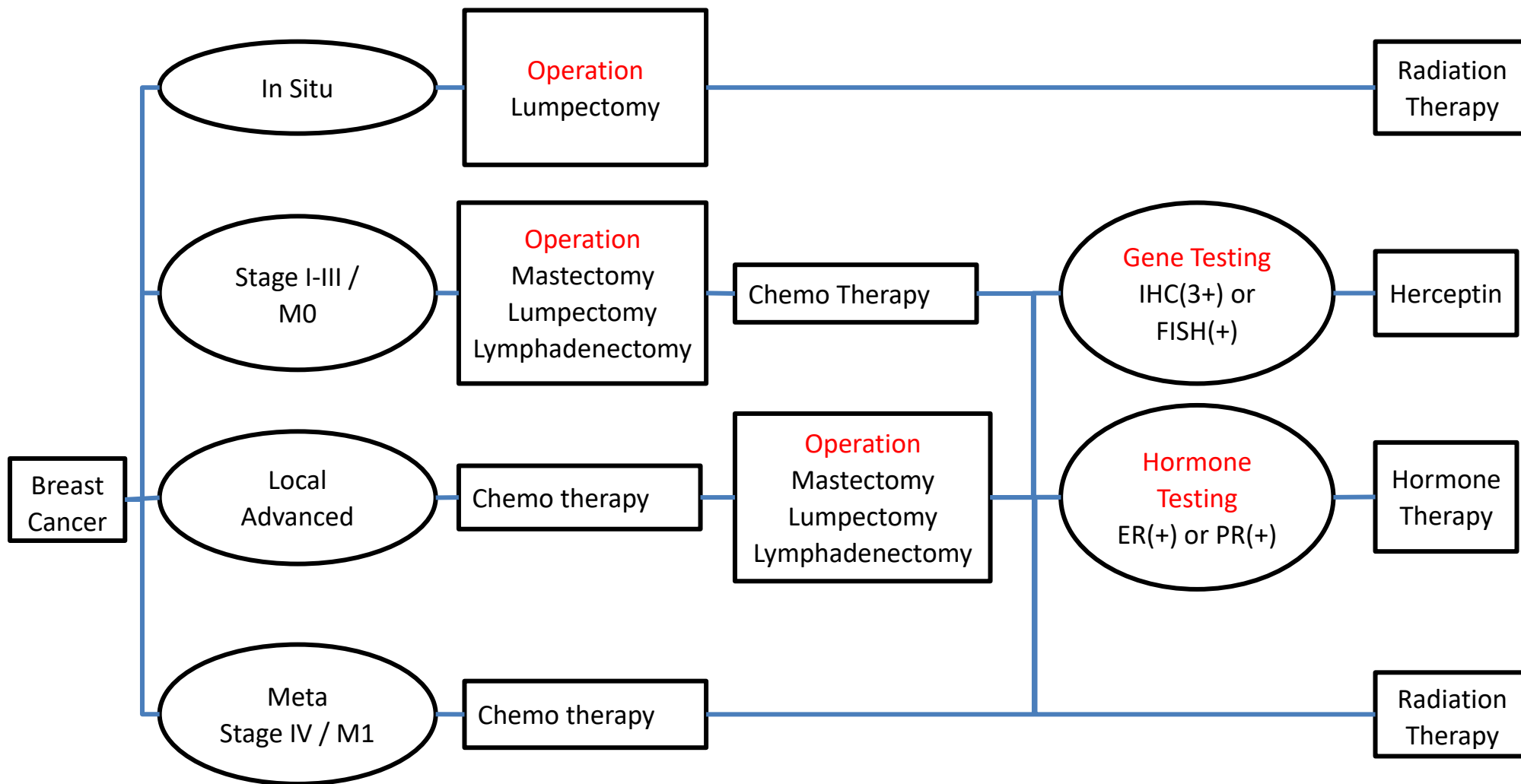
Figure 1. Breast cancer treatment regimen
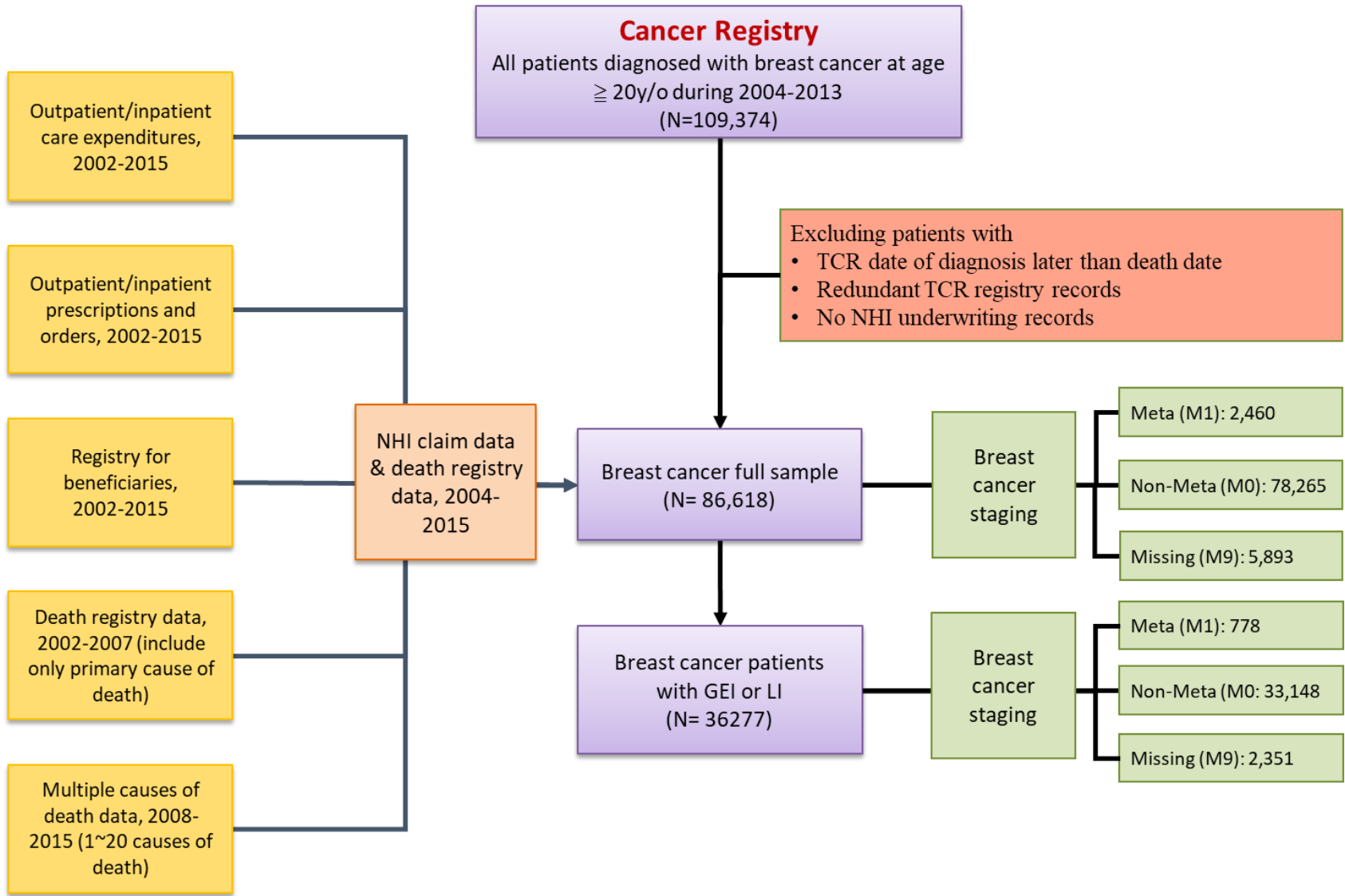
Figure 2. Sample construction
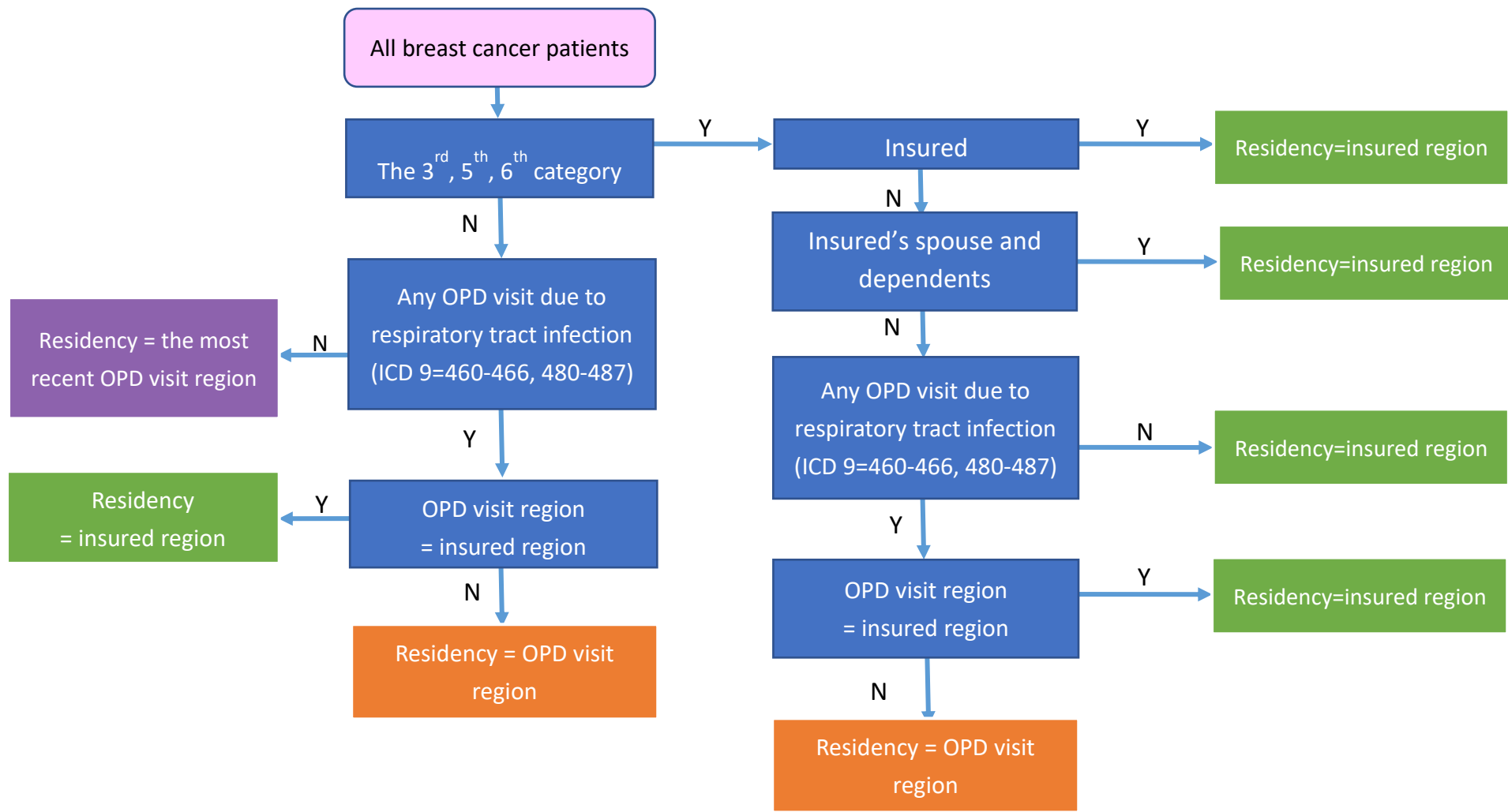
Figure 3. Residency proxy

Source: Lin et al. (2011)

Note: Insured region is the location of NHI enrollment

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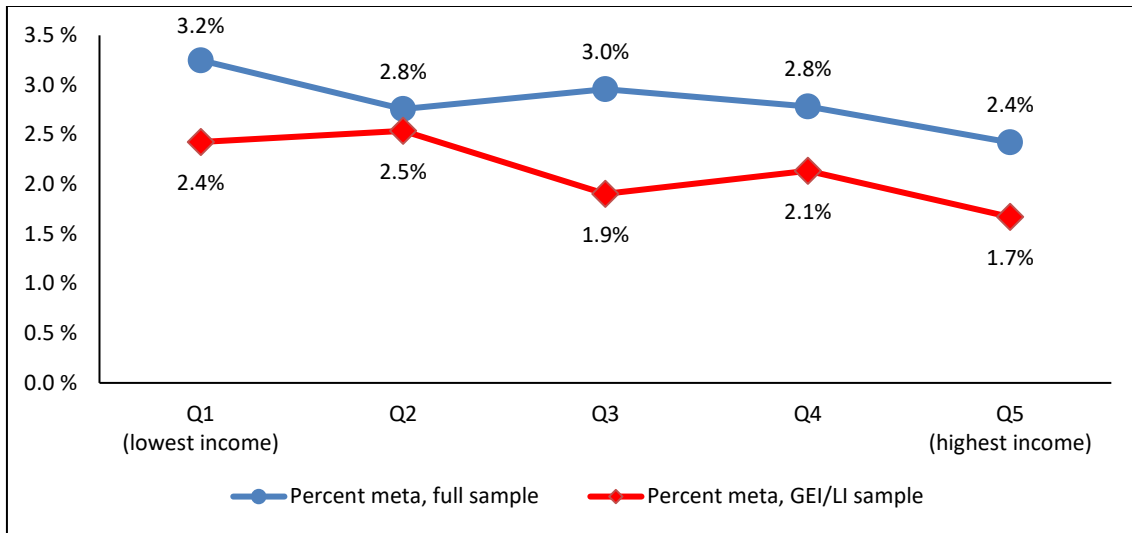
Figure 4A. Percentage of breast cancer patients with metastasis at diagnosis, by income quintile
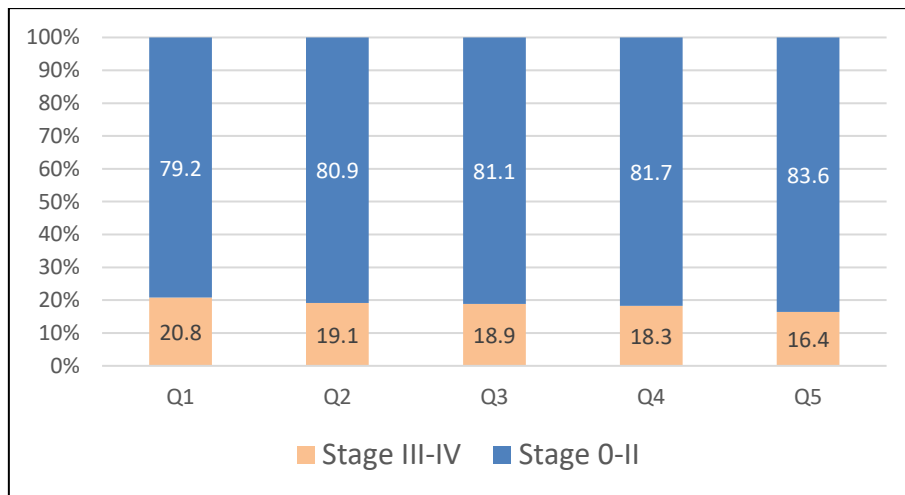
Figure 4B. Cancer stage by income quintile, full sample
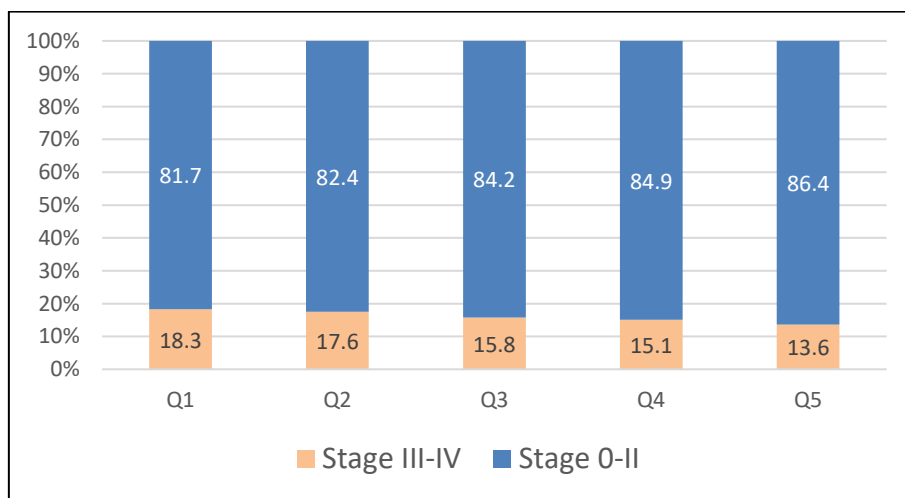
Figure 4C. Cancer stage by income quintile, GEI/LI sample
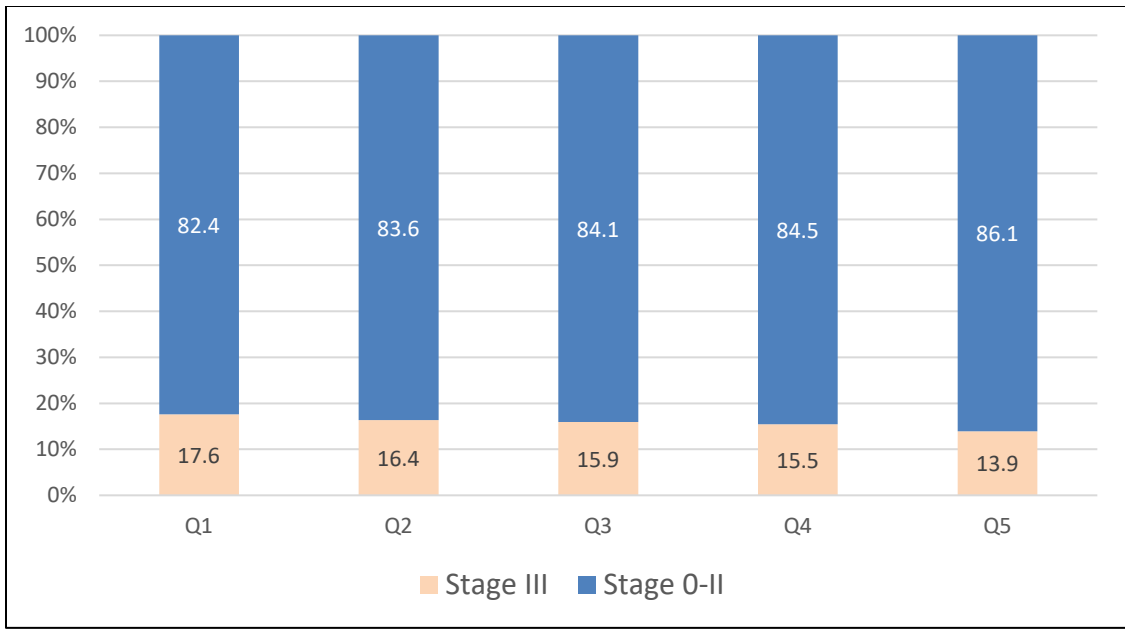
Figure 5A. Percentage of breast cancer patients diagnosed Stage 0-II and III by income quintiles in the full sample, 2004-2013
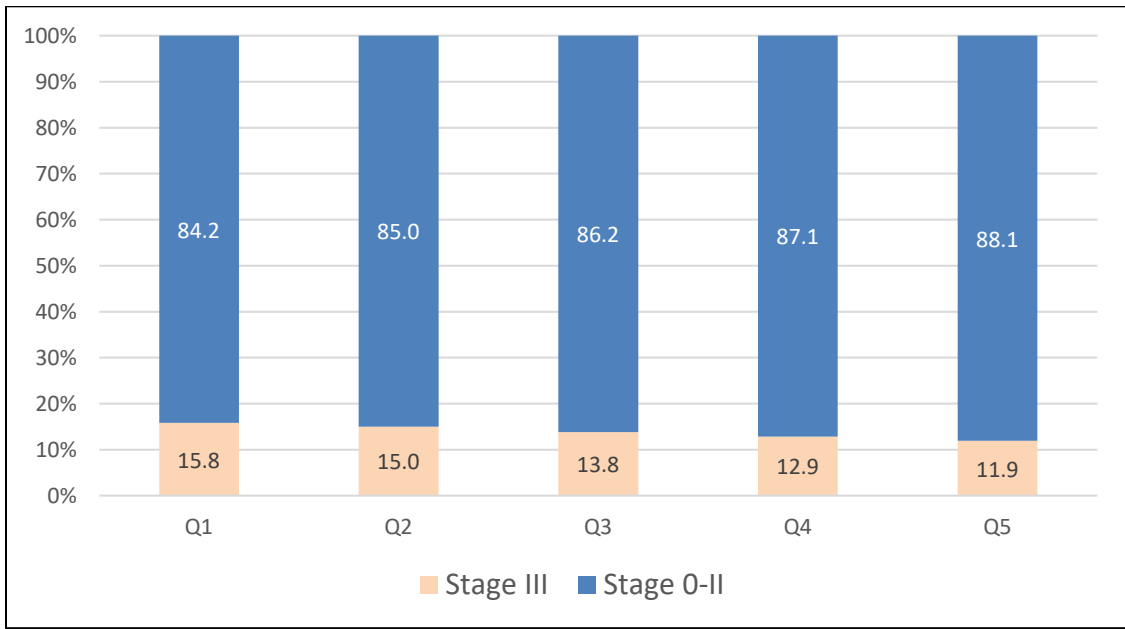
Figure 5B. Percentage of breast cancer patients diagnosed Stage 0-II and III by income quintiles in the GEI/LU sample, 2004-2013
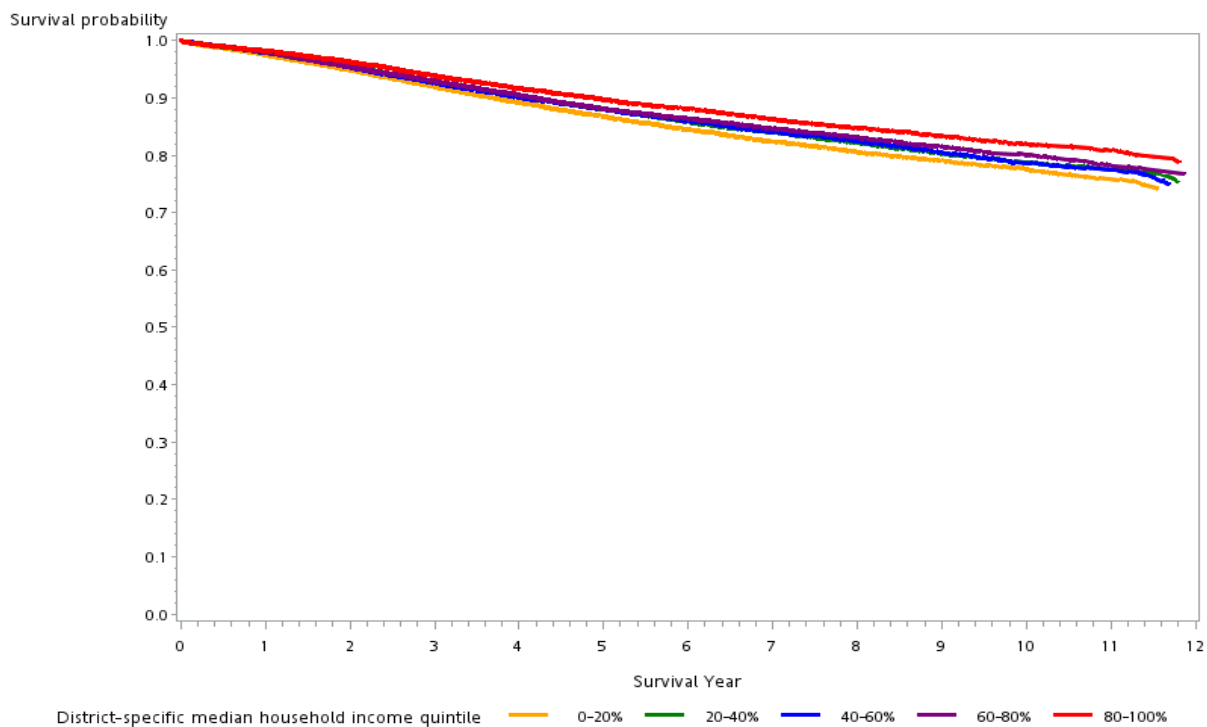
Figure 6A. Survival curves by income quintiles for full sample, adjusted for age and CCI
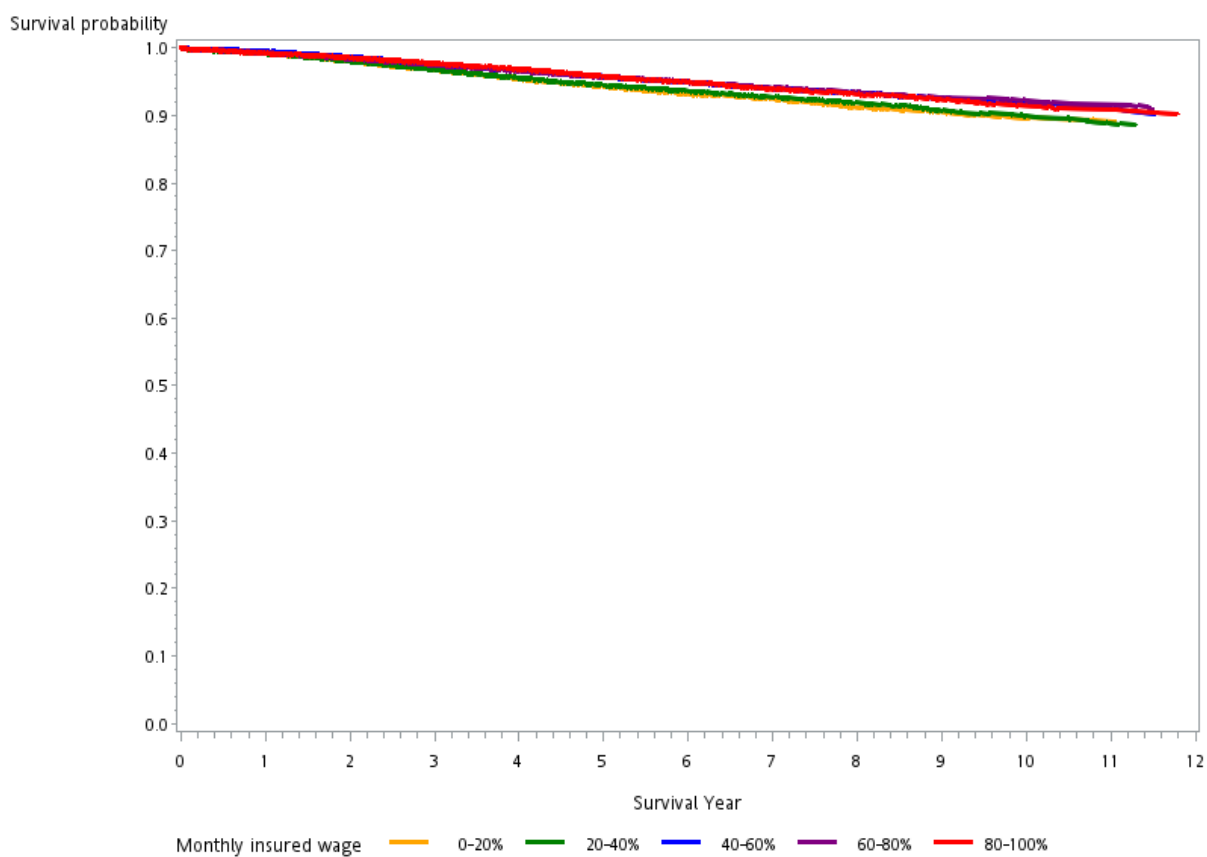
Figure 6B. Survival curves by income quintiles for GEI/LI sample, adjusted for age and CCI
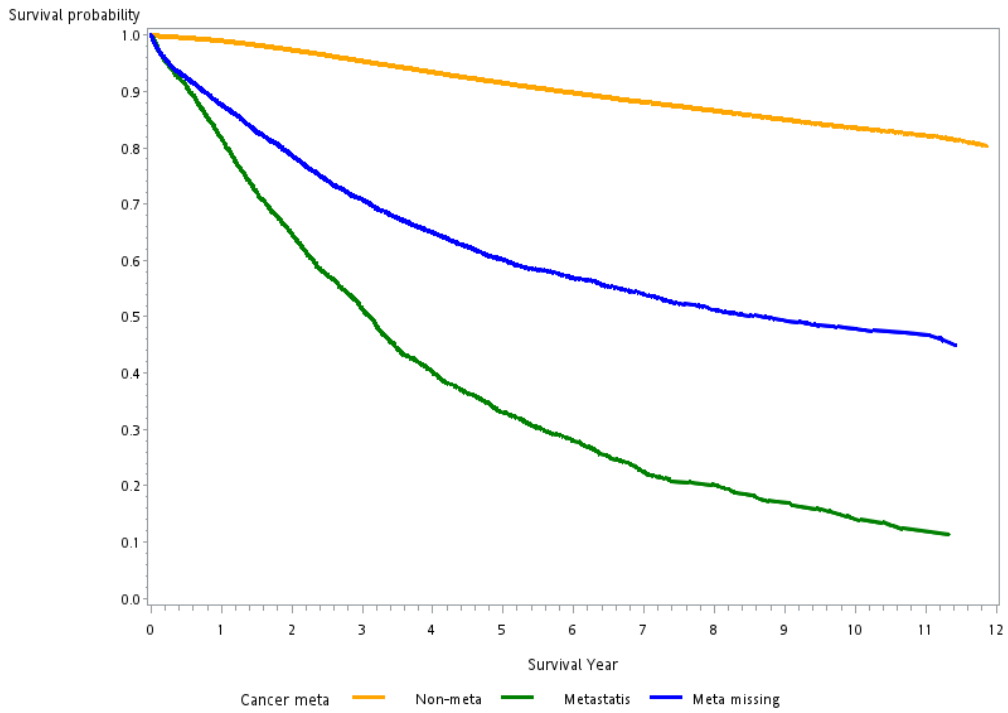
Figure 6C. Survival curves by cancer metastasis status for full sample, adjusted for age and CCI

Figure 7A. Probability of receiving trastuzumab by income quintiles among stage III & IV patients of the full sample diagnosed between 2004 and 2013
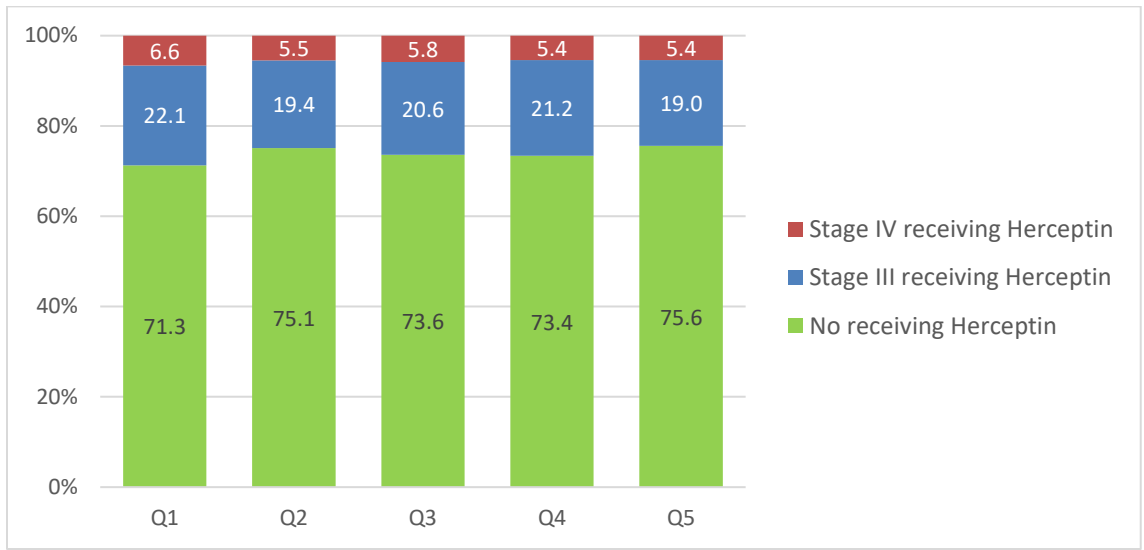
Figure 7B. Probability of receiving trastuzumab by income quintiles among stage III & IV patients of the GEI/LI sample diagnosed between 2004 and 2013
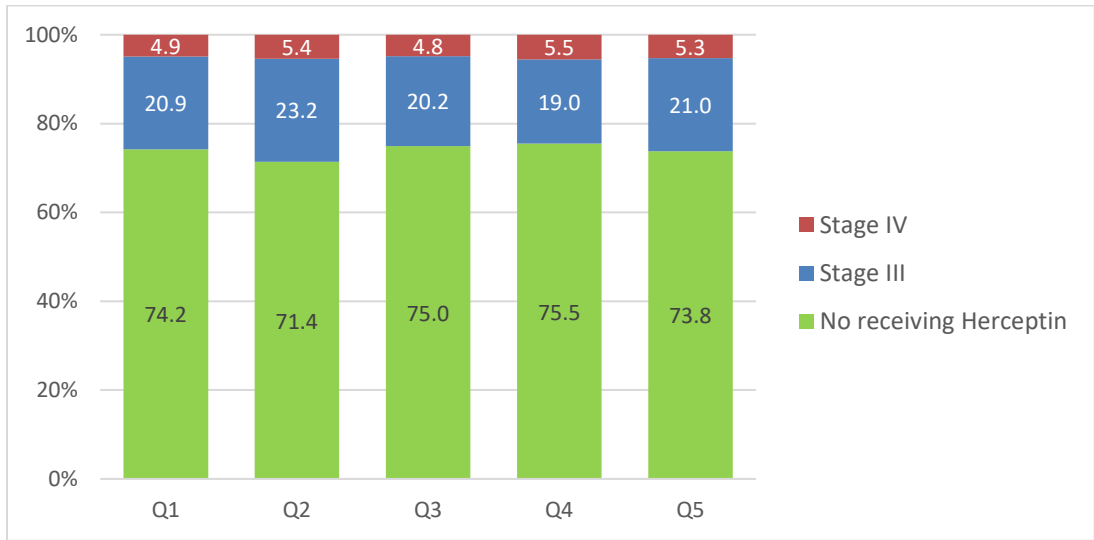
Table 1. Baseline characteristics of all breast cancer patients

	Full sample				GEI/LI sample			
	n=86,618				n=36,277			
	n	(%)	mean	SD	n	(%)	mean	SD
Age diagnosed (yrs/o)	86,618	(100.00)	53.46	±11.8	36,277	(100.00)	50.24	±10.3
Age group distribution								
20-29	914	(1.06)			282	(0.78)		
30-39	7,741	(8.94)			4,464	(12.31)		
40-49	26,415	(30.50)			14,017	(38.64)		
50-59	27,556	(31.81)			11,515	(31.74)		
60-69	14,977	(17.29)			4,209	(11.60)		
70-79	6,766	(7.81)			1,394	(3.84)		
80-89	2,039	(2.35)			362	(1.00)		
90+	210	(0.24)			34	(0.09)		
Residency by NHIA division office								
Taipei	34,690	(40.05)			16,195	(44.64)		
Northern	10,374	(11.98)			4,851	(13.37)		
Central	15,331	(17.70)			6,296	(17.36)		
Southern	11,484	(13.26)			3,825	(10.54)		
Kong-pi	13,178	(15.21)			4,618	(12.73)		
Eastern	1,561	(1.80)			492	(1.36)		
Residency[1]								
Non-remote	85,817	(99.08)			36,105	(99.53)		
Remote area	801	(0.92)			172	(0.47)		
Income proxy[2]								
Quintile 1	18,066	(20.86)	527,881	±22,178	7,213	(19.88)	16,549	±415
Quintile 2	18,569	(21.44)	579,035	±15,807	7,050	(19.43)	21,255	±2,418
Quintile 3	15,695	(18.12)	611,025	±7,121	7,465	(20.58)	31,304	±3,158
Quintile 4	18,387	(21.23)	658,229	±20,583	6,957	(19.18)	42,681	±3,019
Quintile 5	15,901	(18.36)	769,906	±61,729	7,592	(20.93)	68,431	±21,098
Year of breast cancer diagnosis								
2004	5,496	(6.35)			2,071	(5.71)		
2005	5,933	(6.85)			2,306	(6.36)		
2006	6,350	(7.33)			2,588	(7.13)		
2007	7,480	(8.64)			3,006	(8.29)		
2008	7,870	(9.09)			3,293	(9.08)		
2009	8,842	(10.21)			3,776	(10.41)		

2010	10,287	(11.88)			4,310	(11.88)	
2011	10,703	(12.36)			4,635	(12.78)	
2012	11,441	(13.21)			4,894	(13.49)	
2013	12,216	(14.10)			5,398	(14.88)	
Cancer overall stage							
0	10,298	(11.89)			4,904	(13.52)	
I	23,200	(26.78)			10,299	(28.39)	
II	25,605	(29.56)			10,254	(28.27)	
III	11,184	(12.91)			4,124	(11.37)	
IV	2,456	(2.84)			776	(2.14)	
Unknown	13,875	(16.02)			5,920	(16.32)	
Breast cancer metastasis							
Non-Meta (M0)	78,265	(90.36)			33,148	(91.37)	
Meta (M1)	2,460	(2.84)			778	(2.14)	
Missing (M9)	5,893	(6.80)			2,351	(6.48)	
Status at the end of the observation period							
Alive	72,315	(83.49)			31,944	(88.06)	
Deceased	14,303	(16.51)			4,333	(11.94)	
Years survived after diagnosis	86,618	(100.00)	5.57	±2.9	36,277	(100.00)	5.69	±2.8
Charlson Comorbidity Index							
Baseline	86,618	(100.00)	0.69	±1.8	36,277	(100.00)	0.50	±1.5
Overall	86,618	(100.00)	4.59	±3.4	36,277	(100.00)	4.15	±3.3

[1] Remote area defined as 17 counties covered by Taiwan Integrated Delivery System (IDS program)

[2] Income proxy: full sample, using district-specific median household income (NTD per year); GEI/LI sample, monthly insured wage (NTD, per month)

Table 2. Charlson Comorbidity Index (CCI) distribution

	Full sample		GEI/LI sample	
	n=86,618		n=36,277	
	n	(%)	n	(%)
CCI at baseline[1]				
0	67,685	(78.14)	30,171	(83.17)
1	4,108	(4.74)	1,196	(3.30)
2	7,918	(9.14)	3,088	(8.51)
3	2,245	(2.59)	592	(1.63)
4	1,025	(1.18)	204	(0.56)
5	435	(0.50)	90	(0.25)
6	288	(0.33)	62	(0.17)
7	169	(0.20)	30	(0.08)
8	1,828	(2.11)	662	(1.82)
9	499	(0.58)	107	(0.29)
10	239	(0.28)	45	(0.12)
11	101	(0.12)	16	(0.04)
12	38	(0.04)	7	(0.02)
13	20	(0.02)	5	(0.02)
14	9	(0.01)	2	(0.01)
15+	11	(0.01)	-	-
CCI overall[2]				
0	6,766	(7.81)	3,455	(9.52)
1	1,358	(1.57)	514	(1.42)
2	32,080	(37.04)	15,731	(43.36)
3	8,590	(9.92)	2,885	(7.95)
4	3,946	(4.56)	1,157	(3.19)
5	1,389	(1.60)	361	(1.00)
6	774	(0.89)	188	(0.52)
7	442	(0.51)	90	(0.25)
8	18,485	(21.34)	8,251	(22.74)
9	6,354	(7.34)	2,019	(5.57)
10	3,226	(3.72)	851	(2.35)
11	1,685	(1.95)	467	(1.29)
12	730	(0.84)	169	(0.47)
13	372	(0.43)	55	(0.15)
14	218	(0.25)	54	(0.15)
15+	203	(0.24)	30	(0.08)

[1] CCI score calculated by comorbidity record before cancer diagnosed

[2] CCI score calculated by comorbidity record in overall observation period

Table 3A. Cancer-related health care utilization and characteristics of prescribing providers, full sample

| | Full sample n=86,618 | | | | | |
| | Trastuzumab | | FISH test | | IHC test | |
	n	(%)	n	(%)	n	(%)
Patient was prescribed this test or therapy						
Yes	9,369	(10.82)	9,909	(11.44)	68,731	(79.35)
No	77,249	(89.18)	76,709	(88.56)	17,887	(20.65)
Ownership of hospital where prescribed						
Public (government-owned)	2,717	(29.00)	3,875	(39.11)	22,538	(32.79)
Foundation-owned (private not-for-profit)	6,377	(68.06)	5,826	(58.80)	44,161	(64.25)
Physician-owned (private)	275	(2.94)	208	(2.10)	2,032	(2.96)
No prescribing	77,249	-	76,709	-	17,887	-
Hospital location by NHIA division office						
Taipei	3,703	(39.52)	4,056	(40.93)	30,276	(44.05)
Northern	1,028	(10.97)	1,088	(10.98)	7,820	(11.38)
Central	1,831	(19.54)	1,976	(19.94)	12,256	(17.83)
Southern	1,309	(13.97)	1,073	(10.83)	7,854	(11.43)
Kong-pi	1,334	(14.24)	1,626	(16.41)	9,739	(14.17)
Eastern	164	(1.75)	90	(0.91)	786	(1.14)
No prescribing	77,249	-	76,709	-	17,887	-
Physician specialty						
Surgery	3,927	(41.91)	6,470	(65.29)	56,398	(82.06)
Hematology & Oncology	4,362	(46.56)	2,081	(21.00)	1,874	(2.73)
Other	1,080	(11.53)	1,358	(13.70)	10,459	(15.22)
No prescribing	77,249	-	76,709	-	17,887	-
Year prescribed						
2004	19	(0.20)	-	-	3,498	(5.09)
2005	103	(1.10)	-	-	4,175	(6.07)
2006	280	(2.99)	-	-	4,662	(6.78)
2007	366	(3.91)	-	-	5,599	(8.15)
2008	453	(4.84)	-	-	5,933	(8.63)
2009	547	(5.84)	1,040	(10.50)	6,894	(10.03)
2010	1,744	(18.61)	1,863	(18.80)	7,931	(11.54)
2011	1,620	(17.29)	1,922	(19.40)	8,496	(12.36)
2012	1,611	(17.20)	2,027	(20.46)	9,353	(13.61)
2013	1,616	(17.25)	2,271	(22.92)	10,299	(14.98)
2014	759	(8.10)	525	(5.30)	1,287	(1.87)
2015	251	(2.68)	261	(2.63)	604	(0.88)
No prescribing	77,249	-	76,709	-	17,887	-

Table 3B. Cancer-related health care utilization and characteristics of prescribing providers, GEI/LI sample

	GEI/LI sample					
	n=36,277					
	Trastuzumab		FISH		IHC	
	n	(%)	n	(%)	n	(%)
Patient was prescribed this test or therapy						
Yes	3,684	(10.16)	4,308	(11.88)	29,389	(81.01)
No	32,593	(89.84)	31,969	(88.12)	6,888	(18.99)
Ownership of hospital where prescribed						
Public (government-owned)	1,144	(31.05)	1,826	(42.39)	10,263	(34.92)
Foundation-owned (private not-for-profit)	2,433	(66.04)	2,398	(55.66)	18,317	(62.33)
Physician-owned (private)	107	(2.90)	84	(1.95)	809	(2.75)
No prescribing	32,593	-	31,969	-	6,888	-
Hospital location by NHIA division office						
Taipei	1,624	(44.08)	1,911	(44.36)	14,311	(48.70)
Northern	469	(12.73)	491	(11.40)	3,586	(12.20)
Central	710	(19.27)	873	(20.26)	4,971	(16.91)
Southern	389	(10.56)	369	(8.57)	2,765	(9.41)
Kong-pi	442	(12.00)	632	(14.67)	3,528	(12.00)
Eastern	50	(1.36)	32	(0.74)	228	(0.78)
No prescribing	32,593	-	31,969	-	6,888	-
Physician specialty						
Surgery	1,576	(42.78)	2,822	(65.51)	24,361	(82.89)
Hematology & Oncology	1,693	(45.96)	888	(20.61)	693	(2.36)
Other	415	(11.26)	598	(13.88)	4,335	(14.75)
No prescribing	32,593	-	31,969	-	6,888	-
Year prescribed						
2004	6	(0.16)	-	-	1,379	(4.69)
2005	37	(1.00)	-	-	1,675	(5.70)
2006	89	(2.42)	-	-	1,932	(6.57)
2007	114	(3.09)	-	-	2,255	(7.67)
2008	147	(3.99)	-	-	2,534	(8.62)
2009	191	(5.18)	459	(10.65)	3,029	(10.31)
2010	712	(19.33)	781	(18.13)	3,384	(11.51)
2011	671	(18.21)	821	(19.06)	3,746	(12.75)
2012	637	(17.29)	889	(20.64)	4,060	(13.81)
2013	664	(18.02)	1,014	(23.54)	4,600	(15.65)
2014	314	(8.52)	232	(5.39)	566	(1.93)
2015	102	(2.77)	112	(2.60)	229	(0.78)
No prescribing	32,593	-	31,969	-	6,888	-

Table 4. Income-related inequality in use of Trastuzumab, IHC, FISH gene-testing and breast cancer metastasis, as measured by concentration index by year of diagnosis

Year of diagnosis	Full sample								
	n	IHC		FISH		Trastuzumab		n	Breast cancer metastasis
		CI		CI		CI			CI
Overall	86,618	0.0247	***	-0.0024		-0.0133	***	80,725	-0.0009 ***
2004	5,496	0.0052		-0.0002		0.0039		5,247	-0.0003
2005	5,933	0.0580	***	-0.0007		-0.0174	***	5,639	-0.0025
2006	6,350	0.0253	*	-0.0011		-0.0113	**	6,023	-0.0025
2007	7,480	0.0316	**	-0.0034	***	-0.0128	***	6,924	-0.0017 **
2008	7,870	0.0224	*	-0.0015		-0.0077	**	7,259	-0.0004
2009	8,842	0.0219	*	-0.0021		-0.0185	***	8,165	-0.0017 **
2010	10,287	0.0284	**	-0.0074		-0.0116	*	9,651	-0.0007
2011	10,703	0.0179	*	-0.0097		-0.0180	**	9,919	0.0000
2012	11,441	0.0209	*	0.0131		-0.0107	*	10,582	-0.0003
2013	12,216	0.0268	***	0.0193	**	-0.0155	***	11,316	-0.0017 **

Year of diagnosis	GEI/LI sample								
	n	IHC		FISH		Trastuzumab		n	Breast cancer metastasis
		CI		CI		CI			CI
Overall	36,277	0.0063		-0.0083	***	-0.0126	***	33,926	-0.0007 **
2004	2,071	0.0079		-0.0028		-0.0089	*	1,994	-0.0033 *
2005	2,306	0.0287		-0.0016		-0.0087		2,196	-0.0012
2006	2,588	0.0043		0.0006		-0.0065		2,470	-0.0047 *
2007	3,006	0.0047		-0.0019		-0.0052		2,806	-0.0010 *
2008	3,293	0.0035		-0.0052	*	-0.0063		3,070	-0.0002
2009	3,776	0.0429	***	-0.0047		-0.0134		3,517	-0.0003
2010	4,310	0.0150		0.0006		-0.0081		4,049	-0.0014 *
2011	4,635	-0.0096		-0.0148		-0.0192	*	4,303	0.0004
2012	4,894	0.0090		-0.0143		-0.0186	**	4,542	-0.0003
2013	5,398	-0.0173		-0.0053		-0.0155	**	4,979	-0.0002

Note: Breast cancer metastasis: the analytical sample excluding patients with M staging missing value; Income proxy: full sample, using district-specific median household income (NTD per year); GEI/LI sample, monthly insured wage (NTD, per month); CI: concentration index.

*: <0.05   **: <0.01   ***: <0.001

Table 5. Income-related inequality in use of Trastuzumab for patients diagnosed before and after coverage expansion, as measured by concentration index

	Full sample			GEI/LI sample		
M0+M1 patients	n=78,265			n=33,926		
Time of diagnosis	n	CI		n	CI	
All	80,725	-0.0124	***	33,926	-0.0112	***
Pre-period[1]	39,046	-0.0107	***	15,976	-0.0076	***
Pre-period[2]	37,241	-0.0028	***	15,249	-0.0027	***
Post-period	41,679	-0.0119	***	17,950	-0.0136	***
M0 patients	n=78,265			n=33,148		
Time of diagnosis	n	CI		n	CI	
All	78,265	-0.0106	***	33,148	-0.0107	***
Pre-period[1]	37,925	-0.0094	***	15,645	-0.0066	***
Pre-period[2]	36,167	-0.0019	***	14,937	-0.0021	***
Post-period	40,340	-0.0098	***	17,503	-0.0138	***
M1 patients	n=2,460			n=778		
Time of diagnosis	n	CI		n	CI	
All	2,460	-0.0616	*	778	0.0605	
Pre-period[1]	1,121	-0.0508		331	0.0230	
Pre-period[2]	1,074	-0.0677	*	312	0.0052	
Post-period	1,339	-0.0585		447	0.0899	

*: <0.05   **: <0.01   ***: <0.001

CI: concentration index

Income proxy: full sample, using district-specific median household income (NTD per year); GEI/LI sample, monthly insured wage (NTD, per month)

Pre-period[1]: year of diagnosis $\leqq$ 2009 for M0, $\leqq$ 2008 for M1

Pre-period[2]: Same definition as Pre-period[1], but excluding patients who received Trastuzumab after 2010 for M0, and 2009 for M1

Table 6. Regression analyses of predictors of Trastuzumab treatment in M0 patients by different samples

	Full sample			Full sample[1]			GEI/LI sample			GEI/LI sample[2]		
	n=78265			n=76507			n=33148			n= 32440		
	β	(S.E.)	M.E.	β	(S.E.)	M.E.	β	(S.E.)	M.E.	β	(S.E.)	M.E.
Age diagnosed	-0.0086	(0.0011) ***	-0.0006	-0.0080	(0.0012) ***	-0.0003	-0.0035	(0.0020)	-0.0002	-0.0028	(0.0022)	-0.0001
CCI at baseline	0.0188	(0.0080) *	0.0012	0.0181	(0.0095)	0.0006	0.0249	(0.0145)	0.0017	0.0190	(0.0175)	0.0005
Residency (remote vs non-remote)	0.0140	(0.0531)	0.0009	-0.0174	(0.0610)	-0.0005	0.0120	(0.1052)	0.0008	-0.0281	(0.1202)	-0.0008
Post (diagnosed after 2010)	0.4935	(0.0581) ***	0.0320	1.3310	(0.0767) ***	0.0418	0.3563	(0.0846) ***	0.0238	1.3268	(0.1173) ***	0.0373
Income quintile[3]												
Income Q1 (0%-20%)	0.1095	(0.0644)	0.0071	0.0093	(0.0951)	0.0003	-0.0675	(0.0938)	-0.0045	0.0927	(0.1431)	0.0026
Income Q2 (20%-40%)	0.0912	(0.0626)	0.0059	-0.0111	(0.0936)	-0.0003	-0.0004	(0.0941)	0.0000	-0.1572	(0.1550)	-0.0044
Income Q3 (40%-60%)	1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)	
Income Q4 (60%-80%)	0.0630	(0.0622)	0.0041	0.0065	(0.0927)	0.0002	-0.2018	(0.0997) *	-0.0135	-0.2685	(0.1658) *	-0.0104
Income Q5 (80%-100%)	-0.1849	(0.0685) **	-0.0120	-0.3120	(0.1036) **	-0.0098	-0.3606	(0.1022) ***	-0.0240	-0.5276	(0.1702) **	-0.0148
Interaction of income & post												
Income Q1 x Post2010	-0.1039	(0.0778)	-0.0067	-0.0112	(0.1041)	-0.0004	0.1692	(0.1184)	0.0113	0.0112	(0.1603)	0.0003
Income Q2 x Post2010	-0.1158	(0.0784)	-0.0075	-0.0330	(0.1046)	-0.0010	0.0783	(0.1190)	0.0052	0.2354	(0.1713)	0.0066
Income Q3 x Post2010	1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)	
Income Q4 x Post2010	-0.1227	(0.0791)	-0.0080	-0.0790	(0.1046)	-0.0025	0.0831	(0.1274)	0.0055	0.2487	(0.1838)	0.0070
Income Q5 x Post2010	0.0744	(0.0855)	0.0048	0.1796	(0.1153)	0.0056	02801	(0.1296) *	0.0187	0.4418	(0.1879)	0.0124
Residency by NHIA division office												
Taipei	1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)		1.0000	(Ref.)	
Northern	0.0979	(0.0416) *	0.0064	0.0809	(0.0471)	0.0025	0.1256	(0.0601) *	0.0084	0.1204	(0.0686)	0.0034
Central	0.1641	(0.0373) ***	0.0107	0.1361	(0.0424) **	0.0043	0.2777	(0.0525) ***	0.0185	0.2500	(0.0597) ***	0.0070
Southern	0.1798	(0.0394) ***	0.0117	0.1872	(0.0446) ***	0.0059	0.1474	(0.0653) *	0.0098	0.1793	(0.0734) *	0.0050
Kong-pi	0.0538	(0.0389)	0.0035	-0.0296	(0.0447)	-0.0009	0.0563	(0.0621)	0.0038	-0.0352	(0.0720)	-0.0010
Eastern	0.3744	(0.0859) ***	0.0243	0.3706	(0.0961) ***	0.0116	0.5287	(0.1439) ***	0.0352	0.4448	(0.1687) **	0.0125

1. All M0 sample but excluding patients diagnosed with breast cancer before 2010 and who receive Trastuzumab treatment after 2010.

2. All M0 GEI/LI samples but excluding patients diagnosed with breast cancer before 2010 and who receive Trastuzumab treatment after 2010.

3. Income proxy: full sample, using district-specific median household income (NTD per year), setting middle income quintile group(Q3) as reference group; GEI/LI sample, monthly insured wage (NTD, per month), setting lowest income and district insured people as reference group(Q1)

Table 7. Regression analyses of predictors of Trastuzumab treatment in M1 patients by different samples

	Full sample			Full sample[1]			GEI/LI sample			GEI/LI sample[2]		
	n=2,460			n=2,413			n=778			N=759		
	β	(S.E.)	M.E.	β	(S.E.)	M.E.	β	(S.E.)	M.E.	β	(S.E.)	M.E.
Age diagnosed	-0.0076 (0.0038)	*	-0.0015	-0.0061 (0.0039)		-0.0011	0.0003 (0.0076)		0.0001	0.0019 (0.0078)		0.0004
CCI at baseline	-0.0467 (0.0140)	***	-0.0091	-0.0419 (0.0144)	**	-0.0077	-0.0263 (0.0252)		-0.0060	-0.0175 (0.0261)		-0.0035
Residency (remote vs non-remote)	-0.2549 (0.1881)		0.0498	0.2361 (0.1911)		0.0432	-0.4577 (0.4117)		-0.1035	-0.4291 (0.4148)		-0.0868
Post (diagnosed after 2009)	0.3941 (0.1973)	*	0.0769	0.5677 (0.2098)	**	0.1038	-0.2325 (0.3569)		-0.0526	-0.1546 (0.4045)		-0.0313
Income quintile												
Income Q1 (0%-20%)	-0.0927 (0.2229)		-0.0181	-0.0179 (0.2338)		-0.0033	-0.5888 (0.3720)		-0.1332	-0.6232 (0.4200)		-0.1261
Income Q2 (20%-40%)	-0.1264 (0.2216)		-0.0247	-0.1062 (0.2359)		-0.0194	-0.4792 (0.3732)		-0.1084	-0.3145 (0.4035)		-0.0636
Income Q3 (40%-60%)	1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)		
Income Q4 (60%-80%)	-0.1548 (0.2196)		-0.0302	-0.3342 (0.2421)		-0.0611	-0.2001 (0.3870)		-0.0453	0.1309 (0.4024)		0.0265
Income Q5 (80%-100%)	-0.1703 (0.2225)		-0.0332	-0.2244 (0.2400)		-0.0410	-0.6109 (0.4073)		-0.1382	-0.9364 (0.4985)		-0.1894
Interaction of income & post												
Income Q1 x Post2009	0.1584 (0.2740)		0.0309	0.0666 (0.2854)		0.0122	0.8718 (0.4964)		0.1972	1.1298 (0.5524)	*	0.2286
Income Q2 x Post2009	0.04905 (0.2828)		0.0096	0.0161 (0.2962)		0.0029	0.7280 (0.5016)		0.1647	0.7721 (0.5431)		0.1562
Income Q3 x Post2009	1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)		
Income Q4 x Post2009	0.0931 (0.2844)		0.0182	0.2734 (0.3022)		0.0500	0.5575 (0.5104)		0.1261	0.5340 (0.5349)		0.1080
Income Q5 x Post2009	0.2614 (0.2843)		0.0510	0.2878 (0.2999)		0.0526	1.0966 (0.5234)	*	0.2480	1.6280 (0.6131)	**	0.3294
Residency by NHIA division office												
Taipei	1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)			1.0000 (Ref.)		
Northern	-0.0397 (0.1606)		-0.0087	-0.1080 (0.1675)		-0.0197	0.0903 (0.2537)		0.0204	-0.0438 (0.2721)		-0.0089
Central	0.2728 (0.1364)	*	0.0533	0.2786 (0.1387)	*	0.0510	0.1216 (0.2175)		0.0275	0.1885 (0.2225)		0.0381
Southern	0.0747 (0.1450)		0.0146	0.0457 (0.1485)		0.0084	0.2491 (0.2401)		0.0564	0.3238 (0.2463)		0.0655
Kong-pi	-0.1089 (0.1373)		-0.0213	-0.1900 (0.1419)		-0.0347	-0.2392 (0.2514)		-0.0541	-0.3025 (0.2629)		-0.0612
Eastern	0.4623 (0.3509)		0.0902	0.4160 (0.3587)		0.0761	1.0376 (0.7860)		0.2347	1.0957 (0.7865)		0.2217

1. All M1 sample but excluding patients diagnosed with breast cancer before 2009 and receiving Trastuzumab treatment after 2009.

2. All M1 GEI/LI samples but excluding patients diagnosed with breast cancer before 2009 and receiving Trastuzumab treatment after 2009.

3. Income proxy: full sample, using district-specific median household income (NTD per year), setting middle income quintile group(Q3) as reference group; GEI/LI sample, monthly insured wage (NTD, per month), setting lowest income and district insured people as reference group(Q1)

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