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

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Abstract: The high costs of precision medicine raise the concern that their clinical use will exacerbate income-related disparities in healthcare utilization and health outcomes, especially in resource-poor settings. We study treatment of HER2-positive breast cancer in Taiwan between 2004 and 2015 as a case study of disparities associated with personalized medicine. Analyzing a unique dataset linking medical claims, cancer registry data and proxies for household and area-level income, we find that lower-income patients are more likely to be diagnosed with later stages of cancer, and this pattern renders NHI coverage of target therapy pro-poor even before coverage of the diagnostic test. Moreover, the expansion of NHI coverage—including the FISH diagnostic test and target therapy for early-stage breast cancer—strengthened the pro-poor distribution of genetic testing and target treatment, albeit only marginally. Our regression analyses also confirmed the hypothesis that conditional on having late stage or metastatic breast cancer and controlling for income, the proportion receiving target therapy decreases with geographic remoteness. Taiwan's experience illustrates that personalized medicine can disproportionately benefit the poor even when introduced without coverage of the companion diagnostic test, although geographic and other disparities may persist.

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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. Taiwan, as a prototypical "Asian tiger," has a National Health Insurance (NHI) system straining to finance universal health coverage under pressures of rising population expectations and the ever-increasing capabilities of medicine. This study examines the Taiwan experience over the past decade with incorporating PPM into NHI coverage and its implications for disparities in treatment.

The costs associated with precision medicine treatment have raised the concern that their introduction and spread in clinical use might exacerbate income-related disparities in healthcare resource use and clinical 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, to the extent that poorer patients with cancer may 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, Trastuzumab (Herceptin) for human epidermal growth factor receptor type 2 (HER2)-positive metastatic breast cancer.

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 is still 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 Herceptin 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. The affordability of precision medicines is unsurprisingly a larger 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 this year. Although the testing had been covered by most insurance programs earlier, and Roche started a patient assistance program in 2011,[2] until recently only around half of breast cancer patients in China were tested and only about 30 percent of HER2+ patients were able to use Herceptin for treatment (Hicks, Liu, and Zhao, 2011). Herceptin was added to the insurance reimbursement list in July 2017 along with several other leading cancer drugs as part of a negotiated

[2] "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

reduced-price agreement between pharmaceutical firms and China's Ministry of Human Resources and Social Security (Jourdan 2017).

There is also an interplay of coverage decisions with development of the biotech industry in the region. For example, the Korean Ministry of Food and Drug Safety approved coverage for a biosimilar to Herceptin, Herzuma, in 2014, produced by a South Korean biotech company Celltrion; commercialization was delayed by a Roche patent infringement lawsuit, but Seoul Central District Court 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.[3]

As for many other policy authorities in the region, the Taiwan National Health Insurance Administration (NHIA) confronts some controversies in setting its reimbursement policy for precision medicines -- predominantly target therapies for cancer. At this point, Taiwan NHIA only reimburses a limited number of target therapies for cancer patients, for two reasons: first, these treatment regimens are high cost, generally without sufficient evidence (within a 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. Interestingly, one approach to expanding coverage has been to cover the PPM therapy but require the pharmaceutical firm to cover the costs of the companion diagnostic test. Accordingly, the cost of genetic testing for lung cancer, colorectal cancer and leukemia is paid by the pharmaceutical firm supplying the treatment, or occasionally by the patient's own out-of-pocket payments or by the provider's medical research fund on a case-by-case basis.

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 the fifth leading cause of cancer-related deaths worldwide and is the primary cause of cancer-related death among women (Cancer Research UK, 2014). In 2012, there were 1.7 million new cases of female breast cancer

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

worldwide, 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 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.

In Taiwan, the breast cancer incidence among females was 69.1 per 100,000 in 2013, almost three-fold greater than the reported incidence in Asia, consistent with its higher income and rapid economic transition. 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, although geographic disparities may be more difficult to eradicate. The medical utilization for diagnostic tests and treatment therapies from NHI claims data can be linked to the cancer registry by using the unique national ID created by the MOHW Health and Welfare Data Science Centre. Using this 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. Specifically, 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 other words, we ask 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 fluorescence in-situ hybridization (FISH) test, as well as the 2010 coverage of Herceptin treatment for early-stage breast cancer. 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 stage for which target treatment was first developed and covered), and that even with full coverage, geographic disparities may linger. We find empirical support for both of these conjectures.

The remainder of the paper is organized as follows. First, we provide an overview of Taiwan's health system, the epidemiology of breast cancer in Taiwan, and 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

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), 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 where public hospitals only account 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.

NHI revenue mainly relies on payroll-based premiums, supplemented by a levy on non-payroll income and government subsidies. In 2016, NHI spent roughly NTD 565.6 (USD 18.9) billion on medical claims, accounting for approximately 52% of national health expenditures, and in total, Taiwan devoted 6.6% of GDP to health. As a single payer, NHIA has effectively exploited its market power to experiment with various payment reforms in its 20-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.

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 100,00), 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 an interesting trend among Asian countries, where breast cancer is characterized by a younger age of tumor onset (Shen, 2015). 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). Conversely, mortality rates have decreased by twofold in Western countries during same time period. (World Cancer Research Fund, 2015). 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 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 FISH (since 2009) for breast cancer. 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.

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; in addition, per NHI guidelines, one needs a positive testing result before target therapy treatment can be covered. So the hypothesis that we are testing is that after NHI covers testing as well as treatment, the probability of targeted treatment will less significantly differ with income quintile (i.e., will be more pro-poor than it was before the coverage of the test). In the limit, universal 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 or more aggressive form of cancer that the targeted therapy is most effective in treating. The next section presents our hypotheses with greater precision, using a simple model.

Simple model articulating our hypotheses

Let h represent the probability that an individual with breast cancer has the HER2-positive breast cancer variant and thus would benefit from anti-HER2 target therapy. We assume that all Taiwanese have the same basic genetic propensity and therefore that h is constant, independent of socioeconomic status (SES). The expected value of target therapy, EV, depends on the individual's clinical appropriateness as well as the willingness to pay for the treatment given income *y* and NHI coverage policies. For example, prior to 2009, coverage was conditional on having metastatic HER2-positive breast cancer. Let $\omega(\mathrm{y})$ represent the probability that the patient has metastatic breast cancer at initial diagnosis (M1). Unlike h, this probability is a function of income, because the likelihood breast cancer is detected at an early stage is increasing in income: $\omega'(\mathrm{y}) < 0$. We see

this tendency for higher-SES patients to receive diagnosis and treatment at earlier stages of cancer in the data, in Taiwan and globally.[4]

Let *m* represent spending (resource use) for target therapy treatment and V(m) the patient utility from such treatment:

$$V(m) = yv(m) - \theta m$$

where v(m) captures clinical benefits (increasing at a decreasing rate, $\mathrm{v}'(\mathrm{m}) > 0, \mathrm{v}''(\mathrm{m}) < 0$). For services covered by insurance, θ is the patient co-insurance rate ($0 \leq \theta < 1$, equal to 0 when fully covered by NHI); θm captures the copayment burden on the patient and her household.

NHI coverage of target therapy, but not the 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 θ =0 if the patient had metastatic breast cancer and was HER2-positive. In 2009, this deductible was removed (the FISH test was fully covered) for metastatic cases. Following on the heels of that policy change, in 2010 NIH removed the requirement of having metastatic cancer to qualify for target treatment. Thus by 2010 Taiwan's coverage changed from "top-up" to full coverage for all HER2-positive breast cancer patients, regardless of stage.

[4] For example, in the US, African American women present at more advanced stages of breast cancer (Daly and Olopade 2015 and sources cited therein). 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 a 15% diagnosis rate 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. 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.

The expected value of NHI-coverage for target therapy before 2010 depended on the probability of having metastatic breast cancer:

$$EV(m) = h\ \omega(\mathrm{y})[yv(m) - \theta m]$$

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 relationship with SES: poorer patients benefit more to the extent that they are more likely to be metastatic cases at diagnosis (i.e, the first term $h\ \omega(\mathrm{y})$ is higher to low-income patients); but richer patients benefit more to the extent that they have higher willingness and ability to pay for target therapy (the second term $yv(m) - \theta m$). Thus, *a priori* it is unclear whether the concentration index will be positive or negative[5]; it is an empirical question we address in this study.

Hypothesis #1: The overall association between patient income and receipt of target therapy may be positive or negative, and 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).

Conditional on having HER2-positive breast cancer, a patient's demand for target therapy follows the first order condition setting the marginal clinical benefits equal to the copay "scaled by" income: $\mathrm{v}'(\mathrm{m}) = \frac{\theta}{\mathrm{y}}$. This model captures the tendency for a patient with higher income to be more likely to buy diagnostic tests and treatment with personalized medicine, when those therapies are only partially covered by insurance ($\theta > 0$). Higher income leads to choice of more resource use for targeted therapy: $\frac{dm^*}{dy} = -\frac{\theta}{y^2 v''} > 0$; better insurance coverage (reduction in copay) increases demand for treatment: $\frac{dm^*}{d\theta} = \frac{1}{yv''} < 0$; and the increase in demand from insurance coverage is a smaller absolute magnitude when income is higher, so that a given reduction in copay will have a

[5] More formally, there is an ambiguous sign on the derivative with respect to income of the full expected value including self-pay treatment for early stage HER-positive breast cancer: $EV(m) = h\ \omega(\mathrm{y})[yv(m) - \theta m] + h(1 - \omega(\mathrm{y}))[yv(m) - m]$, and after 2010, EV no longer included the $\omega(\mathrm{y})$ term.

larger impact on the poor than the rich: $\frac{d^2m^*}{dyd\theta} = -\frac{1}{y^2v''} > 0$. Demand is also shaped by geographic access; remote residence could be thought of as decreasing the household's effective income.

Hypothesis #2: Conditional on having late stage or metastatic breast cancer at diagnosis, the proportion receiving target therapy (a) increases with income and (b) decreases with geographic remoteness, controlling for income.

The actual course of treatment will depend not only on patient demand – the patient, after all, does not have full information – but also on provider recommendations. Assume the provider acts as agent for the patient, with the patient utility function an argument in the provider's utility function: $\mathrm{U}(\mathrm{V},\pi) = \alpha V + u(\pi)$, where α captures the degree of agency and π represents net revenue (e.g. a vector of fees multiplied by the number of services provided) with $u'(\pi)>0$.[6] This representation of physician objectives leads to recommendation of testing and treatment according to the following first order condition[7]:

$$\mathrm{v}'(\mathrm{m}^*) = \frac{\theta}{\mathrm{y}} - \frac{u'(\pi)p}{\alpha y}$$

The recommended treatment takes account of the patient co-payment burden as well as patient willingness to pay, and insurance mitigates disparities in treatment. This disparity-reducing effect arises not only because insurance increases ability to pay, especially for the poor; at the extreme, full, first-yuan coverage (a copayment rate of zero) implies no utilization differences by income, unless arising from other dimensions such as knowledge and geographic barriers to access.

[6] $u'' < 0$ implies income effects (diminishing marginal utility of net revenue); we often assume $u'' = 0$ no income effects, with p representing the fee schedule and $\pi = \mathrm{pm}$ representing the net revenue of the provider for a given amount of spending m.

[7] It is also straightforward to model companion diagnostic tests and targeted treatment as two complementary services, $v_{12} > 0$, and to show that if the copayment for service 1 decreases (insurance for genetic diagnostic test), then demand and recommended utilization increase for both services, i.e. both diagnostic test and treatment.

Insurance mitigates disparities also because a provider with some agency for patients ($\alpha > 0$) recommends greater treatment when patients pay less out of pocket ($\frac{dm^*}{d\theta} = \frac{1}{\frac{u''(\pi)p^2}{\alpha} + yv''} < 0$); and the increase in recommended treatment is a smaller absolute magnitude when income is higher, depending on the extent of supply-side incentives and their implications for net revenue.

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

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) 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-term database, 65 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 cases identified in

2004 and later. While we cannot rule out differential coverage by income or other socioeconomic factor, 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 Center. In 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 1 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=77,740) 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. We explored 4 staging variables in the TCR, namely T (tumor size), N (lymph node involvement), M (metastasis, i.e., whether there is evidence that the cancer has traveled to other parts of the body), and the overall stage (Health Promotion Administration, 2016). NHI at first limited Herceptin coverage to those with metastasis and then in 2011 extended the indication for the use of Herceptin to early stage breast cancer

patients (M0, no distant metastasis); therefore, we focus on M staging as the main staging variable in this study. The M staging variable is missing for 8.9% of our analytical sample.

To link up TCR, NHI claims/registration data and death registry data, all the analyses were conducted at the Health and Welfare Data Science Data 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 major 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 household 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). 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, we use the reported monthly insured wage in the NHI Registry of Beneficiaries (hereafter, the GEI/LI sample).

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 2) (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, for people with negative IHC testing results), it is most relevant to limit to patients with meta-static 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 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 Herceptin 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, to examine 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.

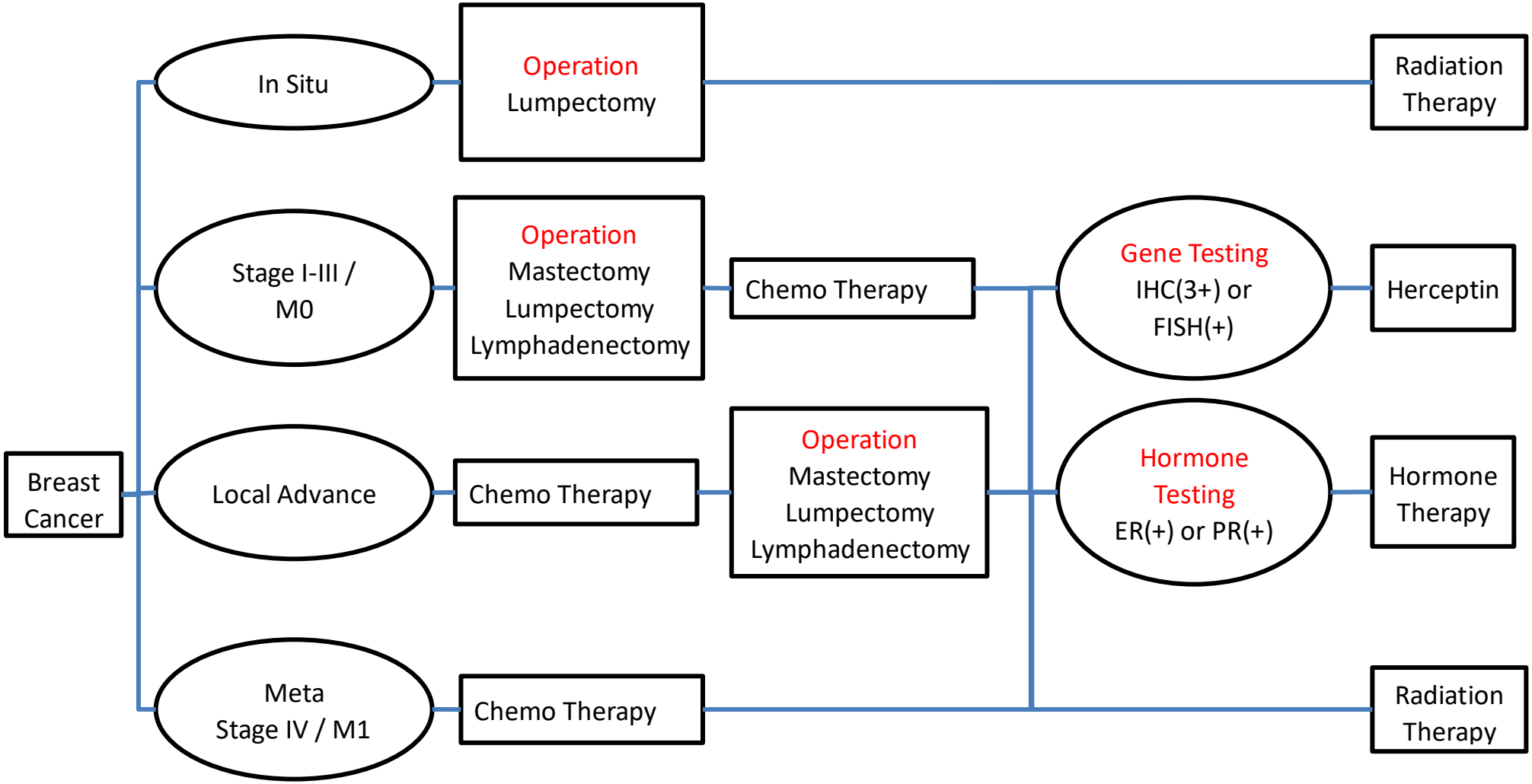


Figure 1. Breast cancer treatment regimen

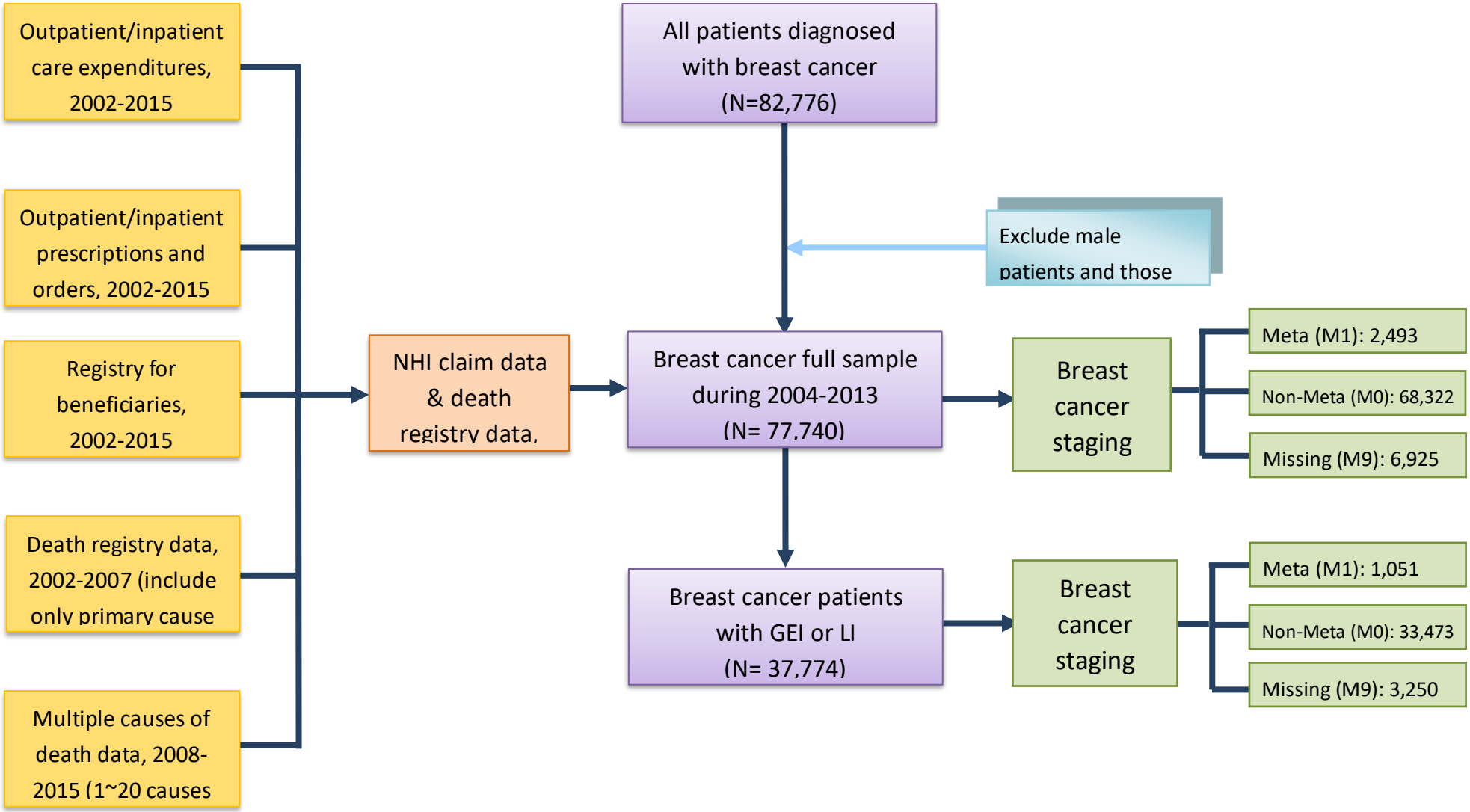


Figure 2. Sample construction

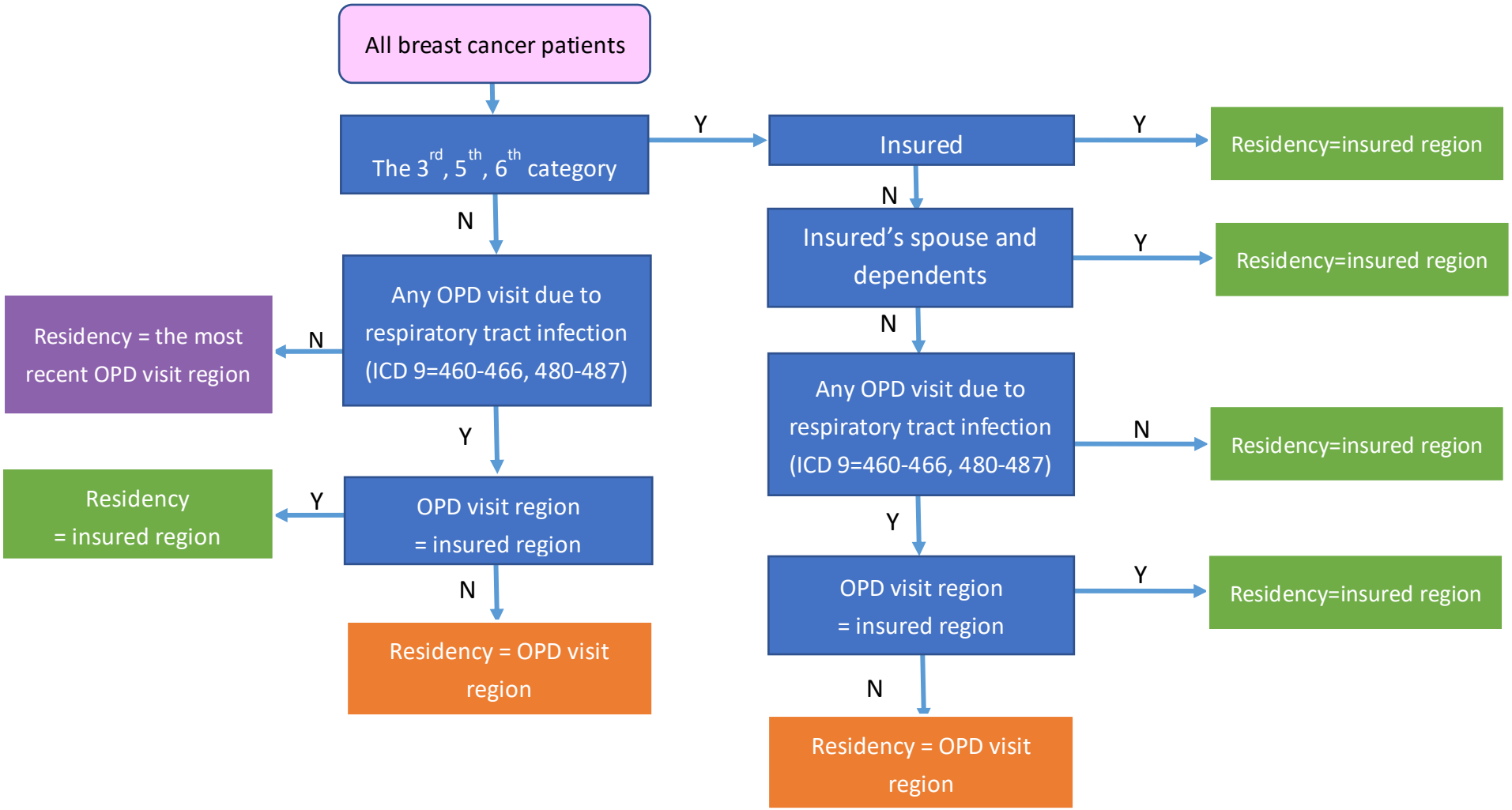
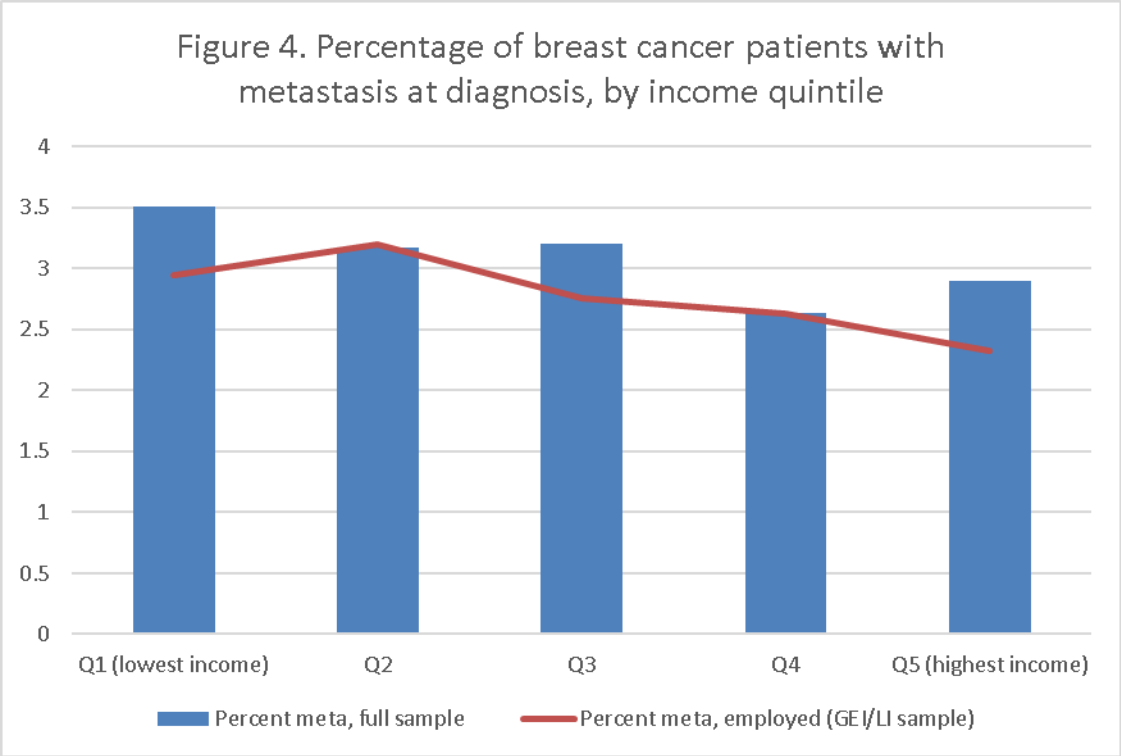


Figure 3. Residency proxy

Source: Lin et al. (2011)

Note: Insured region is the location of NHI enrollment



Results

In our analytic sample of breast cancer patients in Taiwan, the year of diagnosis ranges from 2004 to 2013. Roughly 50% of breast cancer patients were diagnosed between the ages of 45 to 59; the mean age at diagnosis was 53.51 years old (51.19 for the GEI/LI sample; see Table 1). 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 (43.7%). The distribution of patients by tumor stage at diagnosis is 5.3% (6.1% for the GEI/LI sample) with tumor localized/in situ (Stage 0); the majority are diagnosed at an intermediate stage, and 3.2% (2.8% for GEI/LI sample) have metastatic breast cancer already at diagnosis (M1). The M staging variable is missing value for 8.6-8.9% of the sample. As hypothesized and consistent with earlier literature, the probability of metastasis at diagnosis is higher for those with lower income (Figure 4).

As shown in Table 1, average years survived is 5.6 years (5.68 years for GEI/LI sample), distributed from 0 to 11.92 years (survival is truncated at 12/2015). Among those in our sample, the year of death ranges from 2004 to 2015; 17.9% of the sample patients (15.1% for GEI/LI sample) died during the observation period (Table 1). The Charlson Comorbidity Index score varies from 0 to 19; approximately 45% (50% for GEI/LI

sample) have a score of 2 and roughly 20% have a score of 8 (Table 2).

We observe that about 95% of sample patients had an IHC test (a general, low-cost test), 13% had the FISH test, and roughly 12% received target therapy with Herceptin (Table 3). 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 Herceptin, most were treated at private non-for-profit hospitals, followed by public hospitals. Regarding the specialty of the primary provider, 78.4% (8.8%) of the sample patients had IHC (FISH) testing managed by a surgeon, compared to 2.3% (2.7%) by an oncologist. However, 5.7% of the sample patients had Herceptin prescribed by an oncologist, and 5.1% by a surgeon (Table 3).

As shown in Figure 5, the survival curve shows that the highest income groups have longer survival. However, the primary differentiator for survival is cancer staging, with metastatic cancer associated with significantly lower survival. 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.

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 Herceptin 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, most of the indices of medical utilization exhibit a pro-poor distribution, though the magnitude tends to be modest except for the use of Herceptin. In particular, the magnitude of the pro-poor inequality in the use of Herceptin becomes stronger over time both for the whole sample and for GEI/LI patients, i.e., those for whom we have the more accurate income proxy based on monthly wage. The use of IHC and FISH testing in general has a proportional distribution (except for 2005 when IHC testing shows a pro-rich distribution). Essentially, no income-related inequality is observed for the M1 sample regarding any service use. Confirming the summary statistics shown in Figure 4, metastasis at initial diagnosis ("BRCA metastasis" column in Table 4) exhibits a marginally pro-poor distribution of late-stage (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 (Table 5). We define the pre-policy period as 2002-2008 to represent the period before FISH was covered by NHIA, except in the case of the non-metastatic sample,

Figure 5. Survival curve by income quintile and metastatis at diagnosis

where the pre-period is 2002-2009 (before the extension of indication to cover patients without metastasis M0). 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). To better observe the policy effect, we also deleted patients diagnosed in the pre-policy years but receiving testing/Herceptin in the post-policy period. The CIs are negative, showing the distribution of the use of Herceptin is pro-poor, both for the full sample and for the GEI/LI sample of patients at all stages of cancer. For those with non-missing codes for metastatic cancer at diagnosis, the M1 sample, the CI are only marginally negative or indistinguishable from zero. Perhaps more importantly, the CIs for the all-stage samples—both the full sample and the employed formal sector workers with a more accurate household-level income proxy—are larger in magnitude in the post-policy period when compared to the pre-policy period (Table 5).

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, co-morbidities, and stage at diagnosis. These descriptive regressions (not shown) confirm that Herceptin treatment is unrelated to regional median income, controlling for metastatic status at diagnosis; and 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 Herceptin use. We find similar results whether or not we include the 1688 patients who were diagnosed prior to the policy change but received the FISH test after the policy change. The only factor consistently negatively associated with Herceptin use was residence in the remote areas of Taiwan. Remote residence was negatively associated with target treatment, controlling for income and other factors, consistent with our second hypothesis (#2b).

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 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 coverage of the companion diagnostic test.

Specifically, we hypothesized that the overall association between patient income and receipt of target 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). We find that the distribution of metastatic cases is indeed marginally pro-poor for both proxies for income, although the magnitude is modest. The overall CI for Herceptin treatment is also negative. 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, the expansion of NHI coverage—including the FISH diagnostic test and of target therapy for earlier stages of breast cancer—strengthened the pro-poor distribution of genetic testing and target treatment. Our regression analyses also confirmed the hypothesis that conditional on having late stage or metastatic breast cancer, the proportion receiving target therapy decreases with geographic remoteness, controlling for income.

The data does not include those who self-pay for target therapy, which almost surely means we underestimate disparities by inability to observe the number of (presumably higher-income) individuals paying entirely out of pocket for testing and target therapy, especially in the early years before the treatment became standard of care for HER2-positive breast cancer. 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, whether or not such therapy was 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.

Future research will also explore potential interactions with supply-side incentives based on specialty of provider, level of accreditation and ownership of the clinic or hospital, as well as contrast the case of breast cancer with lung cancer and colorectal cancer, where pharmaceutical firms pay for the companion diagnostic tests in exchange for NHI coverage of their target therapy.

Table 1. Baseline characteristics of all breast cancer patients

	Full sample			GEI/LI sample		
	All			All		
	n	(%)	mean	n	(%)	mean
Age at diagnosed	**77,740**	**(100.0)**	53.51	**37,774**	**(100.0)**	51.19
20-24	112	(0.1)		62	(0.16)	
25-29	676	(0.9)		379	(1.00)	
30-34	2,178	(2.8)		1,334	(3.53)	
35-39	4,901	(6.3)		3,150	(8.34)	
40-44	9,449	(12.2)		5,751	(15.22)	
45-49	14,050	(18.1)		7,825	(20.72)	
50-54	13,352	(17.2)		6,602	(17.48)	
55-59	11,371	(14.6)		4,994	(13.22)	
60-64	7,901	(10.2)		3,016	(7.98)	
65-69	5,496	(7.1)		1,915	(5.07)	
70-74	3,860	(5.0)		1,235	(3.27)	
75-79	2,348	(3.0)		787	(2.08)	
80-84	1,319	(1.7)		469	(1.24)	
>=85	727	(0.9)		255	(0.68)	
Income proxy*						
Quintile 1	15,791	(20.3)	528,349	7,866	(20.8)	16,545
Quintile 2	16,608	(21.4)	579,075	7,631	(20.2)	22,092
Quintile 3	14,465	(18.6)	610,893	7,977	(21.1)	32,771
Quintile 4	15,366	(19.8)	655,064	7,338	(19.4)	44,240
Quintile 5	15,510	(20.0)	762,152	6,962	(18.4)	66,940
Residency by NHIA division office						
Taipei	30,855	(39.7)		16,520	(43.7)	
Northern	9,607	(12.4)		5,156	(13.7)	
Central	14,064	(18.1)		6,757	(17.9)	
Southern	9,689	(12.5)		3,738	(9.9)	
Eastern	12,020	(15.5)		5,047	(13.4)	
Kong-pi	1,505	(1.9)		556	(1.5)	
Residency						
Non-remote	77,030	(99.1)		37,613	(99.6)	
Remote	710	(0.9)		161	(0.4)	

Cancer overall stage					
0	4,149	(5.3)		2,302	(6.1)
I	22,784	(29.3)		11,765	(31.1)
II	25,392	(32.7)		11,994	(31.8)
III	11,198	(14.4)		5,048	(13.4)
IV	2,492	(3.2)		1,051	(2.8)
Missing	11,725	(15.1)		5,614	(14.9)
Breast cancer metastasis					
Non-Meta (M0)	68,322	(87.9)		33,473	(88.6)
Meta (M1)	2,493	(3.2)		1,051	(2.8)
Missing (M9)	6,925	(8.9)		3,250	(8.6)
Years survived after diagnosed			5.60		5.68
Status at the end of observation					
Alive	63,835	(82.1)		32,071	(84.9)
Deceased	13,905	(17.9)		5,703	(15.1)

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

Table 2. Charlson Comorbidity Index (CCI) distribution at baseline

	Full sample (n=77,740)		GEI/LI sample (n=37,774)	
	n	(%)	n	(%)
CCI at baseline				
0	7,722	(9.9)	4,080	(10.8)
1	664	(0.9)	246	(0.7)
2	35,181	(45.3)	18,832	(49.9)
3	8,017	(10.3)	3,221	(8.5)
4	3,258	(4.2)	1,145	(3.0)
5	871	(1.1)	299	(0.8)
6	470	(0.6)	141	(0.4)
7	271	(0.4)	84	(0.2)
8	15,074	(19.4)	7,497	(19.8)
9	3,735	(4.8)	1,434	(3.8)
10	1,587	(2.0)	540	(1.4)
11	488	(0.6)	139	(0.4)
12	193	(0.3)	48	(0.1)
13	103	(0.1)	38	(0.1)
14	56	(0.1)	18	(0.0)
15	28	(0.0)	6	(0.0)
16+	22	(0.0)	5	(0.0)

Table 3. Provider characteristics

	Full sample (n=77,740)					
	IHC		FISH		Herceptin	
	n	(%)	n	(%)	n	(%)
Prescribed						
Yes	73,419	(94.4)	10,211	(13.1)	9,278	(11.9)
No	4,321	(5.6)	67,529	(86.9)	68,462	(88.1)
Hospital ownership						
Public	23,344	(30.0)	3,849	(5.0)	2,709	(3.5)
Private non-for-profit	44,058	(56.7)	5,873	(7.6)	6,013	(7.7)
Private for-profit	6,017	(7.7)	489	(0.6)	556	(0.7)
No prescribing	4,321	(5.6)	67,529	(86.9)	68,462	(88.1)
Physician specialty when prescribing						
Surgery	60,913	(78.4)	6,840	(8.8)	3,944	(5.1)
Hematology & Oncology	1,744	(2.2)	2,037	(2.6)	4,263	(5.5)
Radiation Oncology	86	(0.1)	98	(0.1)	125	(0.2)
Obstetrics & Gynecology	677	(0.9)	26	(0.0)	14	(0.0)
Other	9,999	(12.9)	1,210	(1.6)	932	(1.2)
No prescribing	4,321	(5.6)	67,529	(86.9)	68,462	(88.1)
Year prescribed						
2004	4,357	(5.9)	-	-	16	(0.2)
2005	5,208	(7.1)	-	-	110	(1.2)
2006	5,567	(7.6)	-	-	282	(3.0)
2007	6,300	(8.6)	-	-	371	(4.0)
2008	6,750	(9.2)	-	-	469	(5.1)
2009	7,488	(10.2)	1,021	(10.0)	541	(5.8)
2010	8,406	(11.5)	1,953	(19.1)	1,695	(18.3)
2011	9,132	(12.4)	2,049	(20.1)	1,619	(17.5)
2012	9,667	(13.2)	2,135	(20.9)	1,624	(17.5)
2013	10,175	(13.9)	2,406	(23.6)	1,631	(17.6)
2014	231	(0.3)	401	(3.9)	684	(7.4)
2015	138	(0.2)	246	(2.4)	236	(2.5)

Table 4. Income-related inequality in use of gene testing and Herceptin, and breast cancer metastasis, 2004-2015

Year of Diagnosis	Full sample						GEL/LI sample						M1 sample			
	N	IHC test	FISH test	Herceptin	BRCA metastasis		N	IHC test	FISH test	Herceptin	BRCA metastasis		N	IHC test	FISH test	Herceptin
		CI	CI	CI	N	CI		CI	CI	CI	N	CI		CI	CI	CI
All years	77,740	-0.0015 *	-0.0042 *	-0.0117 ***	70,815	-0.0008 *	37,774	0.0011	-0.0068 *	-0.0159 ***	34,524	-0.0009 *	2,493	-0.0013	0.0035	-0.0564 *
2004	5,247	-0.0077	-0.0006	0.0028	4,965	0.0031	2,426	0.0020	-0.0021	-0.0095 *	2,301	-0.0033	218	0.0435	0.0009	0.0524
2005	5,807	0.0101 **	-0.0006	-0.0118 **	5,524	-0.0031 *	2,729	0.0018	-0.0019	-0.0071	2,608	-0.0013	237	0.0429	-0.0008	-0.0269
2006	6,156	-0.0047	-0.0002	-0.0103 *	5,874	-0.0016	3,068	0.0016	0.0000	-0.0061	2,932	-0.0056 *	315	-0.0005	-0.0011	-0.1425
2007	6,833	-0.0045	-0.0019	-0.0154 ***	6,155	-0.0009	3,239	-0.0030	-0.0021	-0.0058	2,942	-0.0011	180	-0.0153	0.0009	-0.2071 *
2008	7,221	-0.0032	-0.0022	-0.0041	6,436	-0.0015	3,533	-0.0001	-0.0074 **	-0.0075	3,174	-0.0015	198	-0.0062	-0.0160	0.0935
2009	7,924	-0.0017	-0.0047	-0.0231 ***	7,050	-0.0015 *	3,900	0.0054 *	-0.0030	-0.0217 *	3,491	-0.0004	198	-0.0071	0.0631	-0.0694
2010	8,899	-0.0015	0.0024	-0.0056	7,970	-0.0005	4,254	0.0032	0.0198	-0.0147	3,829	-0.0010	242	-0.0053	-0.0048	-0.0616
2011	9,611	-0.0029	-0.0225 *	-0.0150 *	8,656	-0.0002	4,695	-0.0005	-0.0012	-0.0249 **	4,226	0.0004	273	-0.0001	0.0395	0.0128
2012	9,969	0.0000	0.0088	-0.0104	9,004	0.0001	4,852	0.0017	0.0069	-0.0210 **	4,397	0.0008	297	0.0004	0.0850	-0.0906
2013	10,073	0.0002	0.0152	-0.0106	9,181	-0.0020 *	5,078	0.0009	-0.0069	-0.0209 **	4,624	-0.0007	335	-0.0006	-0.0109	-0.0242

Note: Breast cancer metastasis: the analytical sample excluding patients with M staging missing value; M1 sample covers only patients with metastasis (i.e., those with M staging non-missing and coded as M1). Income proxy: full sample, using median of district household income (NTD per year); GEI/LI sample, reported insured monthly wage (NTD, per month)
*** p<0.001, ** p<0.01, * p<0.05

Table 5. Income-related inequality in the use of Herceptin in pre- and post-policy period

Year of diagnosis	Full sample						GEI/LI sample					
	All		M0		M1		All		M0		M1	
	N	CI	N	CI	N	CI	N	CI	N	CI	N	CI
All years	76,351	-0.0093 ***	66,693	-0.0062 ***	2,447	-0.0558 *	37,167	-0.0138 ***	32,719	-0.0102 ***	1,028	0.0271
Pre-policy period	29,875	-0.0022 ***	33,029	-0.0018 ***	1,102	-0.0450	14,388	-0.0025 **	16,127	-0.0018 **	456	-0.0480
Post-policy period	46,476	-0.0128 ***	33,664	-0.0082 **	1,345	-0.0477	22,779	-0.0206 ***	16,592	-0.0185 ***	572	0.0962

Note: All the samples here exclude cases diagnosed in the pre-policy period and receiving testing/Herceptin in the post-policy period. Pre-policy period is 2002-2008 for all and M1 sample, and 2002-2009 for M0 sample; post-policy period is 2009-2015 for all and M1 sample, and 2010-2015 for M0 sample. Breast cancer metastasis: the analytical sample excluding patients with M staging missing value; M1 sample covers only patients with metastasis;
Income proxy: full sample, using median of district household income (NTD per year); GEI/LI sample, reported insured monthly wage (NTD, per month)
*** p<0.001, ** p<0.01, * p<0.05.

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