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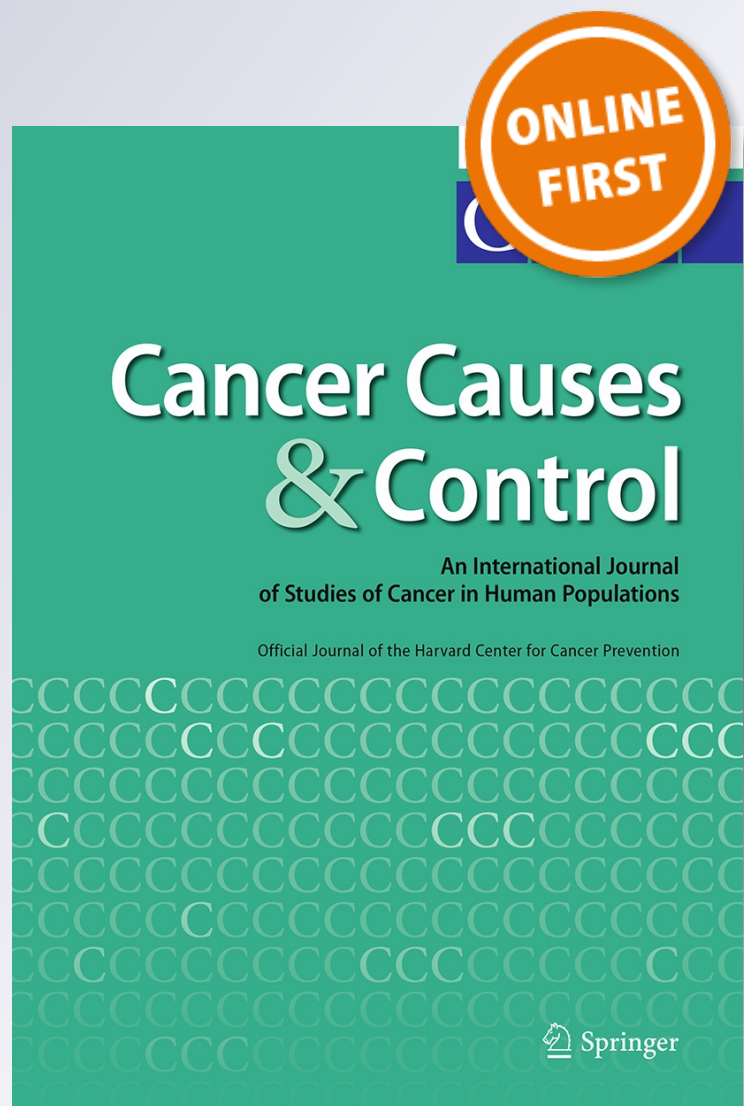Chen, Yingjia S
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ONLINE FIRST

Cancer Causes & Control

An International Journal
of Studies of Cancer in Human Populations

Official Journal of the Harvard Center for Cancer Prevention

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## ORIGINAL PAPER

# Underutilization of gene expression profiling for early-stage breast cancer in California

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## Abstract

*Purpose*  To describe the utilization of gene expression profiling (GEP) among California breast cancer patients, identify predictors of use of GEP, and evaluate how utilization of GEP influenced treatment of early-stage breast cancer.

*Methods*  All women diagnosed with hormone-receptor-positive, node-negative breast cancer reported to the California Cancer Registry between January 2008 and December 2010 were linked to Oncotype DX (ODX) assay results.

*Results*  Overall, 26.7 % of 23,789 eligible patients underwent the assay during the study period. Women age 65 or older were much less likely than women under age 50 to be tested (15.1 vs. 41.4 %, $p < 0.001$). Black women were slightly less likely and Asian women were slightly more likely than non-Hispanic white women to undergo GEP with the ODX assay (22.2 and 28.9 vs. 26.9 %, respectively, $p < 0.001$). Patients residing in low SES census tracts had the lowest use of the test (8.9 %), with the proportion increasing with higher SES category. Women with Medicaid health insurance were less likely than other women to be tested (17.7 vs. 27.5 %, $p < 0.001$). Receipt of adjuvant chemotherapy (ACT) was associated with the ODX recurrence score, although only 63 % of patients whose recurrence scores indicated a high benefit received ACT. Of patients not tested, 15 % received ACT.

*Conclusions*  Nearly three-fourths of eligible breast cancer patients in California during the 3-year period 2008 through 2010 did not undergo GEP. As a result, it is likely that many women unnecessarily received ACT and suffered associated morbidity. In addition, some high-risk women who would have benefited most from ACT were not identified.

**Keywords**  Breast cancer · Cancer registry · Gene expression profiling · Genomics · Chemotherapy

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## Introduction

Most of the more than 200,000 women diagnosed with breast cancer each year in the USA are diagnosed at an early stage of disease when the tumor is still localized [1]. Therapy for women with early-stage breast cancer typically includes surgery and radiation therapy followed by adjuvant endocrine therapy for patients who have hormone-receptor-positive breast cancer. If patients are considered at high risk of recurrence, they are usually also offered adjuvant chemotherapy (ACT). Historically, the decision to treat with ACT has been made using clinical and pathologic features combined with patient and provider

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preferences. Using these guidelines has resulted in many patients receiving ACT even though only a small proportion of them would be expected to have the tumor recur within 5 years without ACT [2]. Approximately 10 % of women receiving ACT suffer side effects serious enough to require an emergency visit or hospitalization [3], which means that many women each year suffer ACT-related toxicities without any likely benefit resulting from such treatment.

In recent years, gene expression profiling (GEP) has become an increasingly used diagnostic tool to evaluate the recurrence risk of cancer and inform treatment decisions. The Oncotype DX (ODX) assay for breast cancer, developed by Genomic Health, Inc. and validated in clinical studies [4], was the first and is currently the most commonly used GEP assay in the USA. Similar assays for breast cancer have been more recently developed by other manufacturers and for other types of cancer.

The ODX assay evaluates expression levels of 21 genes shown to be associated with tumor proliferation, invasion, and estrogen signaling. Results of the assay are combined with a mathematical algorithm to provide a recurrence score that is significantly correlated with the likelihood of distant [5] and loco-regional recurrence [6]. The assay identifies patients who are most likely to benefit from ACT and, importantly, those who will not benefit from ACT [2].

Use of the ODX assay for selected patients is included in guidelines issued by the National Comprehensive Cancer Network (NCCN) [7] and ASCO [4]. Payment for use of the assay was approved by Medicare in 2006 and by California's Medicaid program, Medi-Cal, in 2007; it is also covered by most private insurance carriers. The actual utilization of such assays in women with node-negative, hormone-receptor-positive, and HER2-negative breast cancers, and the use of assay results in determining treatment have not been well quantified. Doing so has important quality of care implications. This project sought to describe the population-based utilization of the ODX assay among eligible breast cancer patients in California, identify predictors of use of the assay, and determine how utilization of the assay influenced treatment of early-stage breast cancer.

## Methods

Eligible cases were defined as stage I or II, node-negative, estrogen or progesterone receptor-positive, and HER2-negative breast cancer diagnosed between January 2008 and December 2010. These cases were identified through the California Cancer Registry (CCR). The CCR, administered by the California Department of Public Health, is the largest statewide population-based cancer registry in the USA and contains demographic, diagnostic, treatment

and outcome information extracted from medical records for every reportable cancer diagnosed among residents of the state since 1988. To identify which patients were assayed with ODX, Genomic Health, the manufacturer of the assay, provided identifiers for women who were tested as well as assay results that were linked to the registry data. Cases also were linked by the California Department of Health Care Services (DHCS) to enrollment information on patients covered by Medi-Cal, the nation's largest state Medicaid program. Enrollment in Medi-Cal was ascertained through 2011 to cover the year after diagnosis when patients would most likely have been tested and have received their first course of treatment.

Demographic and tumor characteristics, as well as first course of treatment information, were extracted from registry data. Race–ethnicity information in the CCR is abstracted from patient medical records and categorized into four major groups: non-Hispanic white, Hispanic, non-Hispanic Asian/Pacific Islander (Asian/PI), and non-Hispanic black. Area-based socioeconomic variables from the 2010 Census were used to create a composite score for five socioeconomic status (SES) levels in the patient's block group of residence. As previously described [8], scores were derived from principal components analysis and combine seven SES indicators: education, blue collar occupation, proportion of workforce without a job, poverty, median income, median rent, and median house value.

Simple descriptive analysis was used to identify characteristics of the patients who met the eligibility criteria for the ODX assay. Patients were categorized as covered by Medi-Cal if they were covered by the program for at least 1 month between 2008 and 2011. Results of the ODX assay were categorized into low (<18), intermediate (18–31), and high (>31) risk scores based on the categories used in the initial validation study [9]. Multivariable logistic regression was used to identify factors associated with utilization of the ODX assay after adjusting for age, race/ethnicity, SES, stage at diagnosis, and Medi-Cal enrollment. The likelihood of ODX utilization was measured by adjusted odds ratios (OR) and their associated 95 % confidence intervals (95 % CI). The SAS System Release 9.3 (SAS Institute Inc., Cary, NC) was used for all data analyses, with a significance threshold of 0.05.

## Results

A total of 23,789 eligible patients were identified (33.4 % of the 71,320 women diagnosed with breast cancer in California during this period). Table 1 shows the demographic characteristics of the study population, as well as whether they underwent the ODX assay. Nearly half

**Table 1** Distribution of patients diagnosed with stage I or II, node-negative, hormone-receptor-positive, and HER2-negative breast cancer, and proportion who received ODX, California, 2008–2010 (n = 23,789)

| | n | % | n underwent testing | % underwent testing | p value |
|---|---|---|---|---|---|
| Age | | | | | <0.001 |
| <50 | 4,152 | 17.45 | 1,718 | 41.4 | |
| 50–64 | 9,095 | 38.23 | 3,033 | 33.4 | |
| 65 | 10,542 | 44.31 | 1,590 | 15.1 | |
| Race/ethnicity | | | | | <0.001 |
| NH White | 16,345 | 68.71 | 4,397 | 26.9 | |
| NH Black | 1,086 | 4.57 | 241 | 22.2 | |
| Hispanic | 3,365 | 14.15 | 833 | 24.8 | |
| Asian/Pacific Islander | 2,789 | 11.72 | 806 | 28.9 | |
| NH American Indian/Other | 204 | 0.86 | 64 | 31.4 | |
| Socioeconomic status | | | | | <0.001 |
| Low | 2,115 | 8.89 | 446 | 21.1 | |
| Low–middle | 3,368 | 14.16 | 779 | 23.1 | |
| Middle | 4,255 | 17.89 | 1,065 | 25.0 | |
| Middle–high | 5,329 | 22.40 | 1,412 | 26.5 | |
| High | 6,138 | 25.80 | 1,895 | 30.9 | |
| Unknown | 2,584 | 10.86 | 744 | 28.8 | |
| Stage at diagnosis | | | | | <0.001 |
| I | 18,385 | 77.28 | 4,701 | 25.6 | |
| II | 5,404 | 22.72 | 1,640 | 30.4 | |
| Medi-Cal coverage | | | | | <0.001 |
| No | 21,780 | 91.55 | 5,985 | 27.5 | |
| Yes | 2,009 | 8.45 | 356 | 17.7 | |

(44 %) were age 65 or older, and more than two-thirds were categorized as non-Hispanic white. Almost half (48.2 %) resided in high or middle–high SES neighborhoods at the time of diagnosis. Eight percent of eligible patients were enrolled in Medi-Cal for at least 1 month. Of these, a substantial majority (64.8 %) were enrolled for the full 48 months; only 12.9 % were enrolled for 6 months or less. Seventy-three percent of Medi-Cal patients were age 65 or older at the time of diagnosis compared to 42 % of non-Medi-Cal patients. Women enrolled in Medi-Cal were less likely to be non-Hispanic white (47.5 vs. 70.7 %) and more likely to reside in census tracts categorized as low SES (22.2 vs. 7.7 %). Medi-Cal patients were slightly less likely to be diagnosed at stage I (72.6 vs. 77.7 %).

Overall, 26.7 % of eligible patients were tested with the ODX assay (Table 1). Women age 65 or older were much less likely than women under age 50 to be tested (15.1 vs. 41.4 %). Black women were slightly less likely and Asian women were slightly more likely than non-Hispanic white women to be tested with the ODX assay (22.2 and 28.9 vs. 26.9 %, respectively). Patients residing in low SES census tracts had the lowest receipt of the assay, with the proportion undergoing the test increasing with higher SES category. Women having Medi-Cal health insurance were less likely than other women to be tested (17.7 vs. 27.5 %).

The proportion of patients assayed did not increase over the time period (28.5 % in 2008, 29.3 % in 2009, 24.1 % in 2010 for non-Medi-Cal patients; 16.4 % in 2008, 20.9 % in 2009, and 15.4 % in 2010 for patients with Medi-Cal).

Table 2 shows the results of the multivariable analysis of predictors of use of the ODX assay among eligible patients. Statistically significant predictors of use included age, race, SES, and stage at diagnosis ($p < 0.0001$). Women age 65 or older had 0.25 times the odds of being tested compared to women under age 50. Black and Hispanic patients were less likely to be tested. Women residing in the lowest SES neighborhoods had 0.66 the odds of being tested compared to those living in high SES neighborhoods to undergo the test. Eligible patients covered by Medi-Cal were slightly less likely to undergo ODX testing after adjustment for SES and other factors, but the differences were not statistically significant.

Results of the assay indicated that nearly 54 % of patients were at low risk of recurrence and would expect a low benefit of ACT (Table 3); nearly 38 % had an unclear benefit; and 8 % were at high risk of recurrence with a high expected benefit of ACT. Receipt of ACT generally followed the expected pattern with patients for whom the score indicated a low benefit of ACT much less likely to receive ACT than patients for whom the test indicated a

**Table 2** Multivariable analysis of predictors of usage of the Oncotype DX assay, California, 2008–2010

|  | Odds ratio | 95 % Wald confidence limits | |
|---|---|---|---|
| **Age** |  |  |  |
| <50 (referent) |  |  |  |
| 50–64 | 0.71 | 0.65 | 0.77 |
| 65 | 0.26 | 0.23 | 0.28 |
| **Race/ethnicity** |  |  |  |
| NH White (referent) |  |  |  |
| NH Black | 0.73 | 0.62 | 0.86 |
| Hispanic | 0.82 | 0.75 | 0.91 |
| Asian/Pacific Islander | 0.91 | 0.83 | 1.00 |
| **Socioeconomic status** |  |  |  |
| Low | 0.66 | 0.58 | 0.75 |
| Low–middle | 0.72 | 0.65 | 0.80 |
| Middle | 0.79 | 0.72 | 0.87 |
| Middle–high | 0.83 | 0.76 | 0.90 |
| High (referent) |  |  |  |
| **Stage at diagnosis** |  |  |  |
| I | 0.81 | 0.75 | 0.87 |
| II (referent) |  |  |  |
| **Medi-Cal coverage** |  |  |  |
| No (referent) |  |  |  |
| Yes | 0.93 | 0.81 | 1.06 |

high benefit. However, only 63 % of patients whose recurrence scores indicated a high benefit received ACT. Patients with Medi-Cal coverage followed a similar pattern but were less likely to receive ACT regardless of ODX score (results not shown). Among patients not tested with ODX, 15.5 % had a record of receipt of ACT.

A multivariable analysis of predictors of receipt of ACT among high-risk patients demonstrated that only age was a statistically significant predictor after adjustment for other factors, with women age 65 and over three times as likely not to receive ACT (OR 3.1, 95 % CI 1.7–5.7). Race, SES, and Medi-Cal coverage were not significant predictors after adjustment for other factors.

## Discussion

Of the approximately 8,000 women diagnosed each year in California with hormone-receptor-positive, node-negative breast cancer, approximately 15 % would be expected to experience a recurrence within 10 years [10]. Accurately predicting which patients are at high risk of recurrence and appropriately managing their care not only improves their prognosis but also spares low-risk patients the expense and toxicity of ACT not likely to improve their outcomes. The results of this study of over 20,000 California women of varied age, race, and socioeconomic status indicate that fewer than 27 % of women eligible for GEP with the ODX assay underwent the test during the study period. This suggests that some women may be receiving chemotherapy they do not need while others who should receive it are not.

The results are similar to those reported in two recently published studies that used data from the population-based SEER program. NCI researchers utilized data from the annual SEER Patterns of Care study that collects additional diagnostic and treatment data for a sample of cancer cases selected from multiple SEER registries. Results from that study showed that utilization of the Oncotype DX test for patients diagnosed with early-stage breast cancer increased from 2.7 % in 2004 to 8.0 % in 2005 and to 27 % in 2010 [11]. Results for older patients in our study population are comparable to those of a recent study of early-stage breast cancer patients aged 65 and older identified through SEER between 2005 and 2009 and linked to Medicare claims. Utilization of the assay for patients categorized as intermediate risk (ER-positive, LN-negative tumors larger than 1 cm) was 26 % in 2009 [12]. This is higher than utilization for patients over age 65 in the current study (15 %), but we did not exclude patients with tumors <0.5 cm for whom the test would not have been indicated, and our patient population is likely to have included a small number of patients with very small tumors. GEP testing also has been reported to be lower in Western states than in Southern or Northeastern regions of the country [12].

**Table 3** Distribution of Oncotype DX recurrence scores for assayed patients and receipt of chemotherapy by risk category for untested and tested eligible breast cancer patients, California, 2008–2010

|  | Recurrence score | | Received chemotherapy | |
|---|---|---|---|---|
|  | n | % | n | % |
| Untested | 17,448 |  | 2,701 | 15.5 |
| Tested | 6,339 |  |  |  |
| <18 (low benefit) | 3,416 | 53.9 | 247 | 7.2 |
| 18–31 (intermediate benefit) | 2,389 | 37.7 | 774 | 32.4 |
| >31 (high benefit) | 534 | 8.4 | 336 | 62.9 |

Utilization of GEP among California breast cancer patients was lower than found at a large academic health center in New York, where 27 % of patients were tested in 2007 and 42 % in 2010 [13]. The patients in the current population-based study were treated in a wide variety of community and academic settings, and it is likely that there is a heterogeneous understanding and acceptance of GEP in these diverse care settings. A small study of women treated at various types of healthcare facilities in New York City between 2006 and 2009 reported that 23 % utilized the ODX assay and that patients who underwent the test were of higher income and more likely to be treated at a tertiary referral center than in a community hospital. Women treated in community hospitals were less likely to be tested even though Medicaid would have covered the cost of the test [14].

We observed a strong association between neighborhood socioeconomic status and utilization of the test, with the odds of testing increasing with socioeconomic status after adjustment for other factors. Prior population-based studies described above reported only a modest association with poverty measured at the census tract level [11, 12], but these studies did not have the size or diversity of our study population. Our area-based SES score contains measures other than income, including employment, housing, and education. Education was shown to be associated with receipt of testing in a registry of over 7,000 patients treated between 2006 and 2008 in a group of comprehensive and community cancer centers [15]. The cost of the test is covered by Medicare and most other health insurance providers, so it is unlikely that cost was a determinative factor in utilization of GEP.

As in other studies, age was a primary predictor both of use of GEP and of receipt of ACT [11, 12, 16]. Older women are more likely to have comorbid illnesses, which could make chemotherapy contraindicated regardless of test results. Comorbidity information was not available in our registry data. The low proportion of older women who underwent the test but did not receive ACT even though their score indicated a high benefit of ACT was surprising, although this is consistent with a prior study, showing that increasing age was associated with decreasing probability of receipt of ACT [16]. A large proportion of older patients covered by Medi-Cal were over age 65 and likely to also be covered by Medicare. These "dual eligible" patients are known to be poorer and sicker than patients covered by either plan alone, and less likely to receive recommended therapy [17].

In contrast to recent results reported from the Carolina Breast Cancer Study for patients diagnosed between 2008 and 2014, we observed lower utilization of GEP among black and Hispanic patients. The researchers on that study were able to adjust for comorbid illnesses, which they observed were more common among nonwhite patients [18].

The distribution of assay results was similar to other studies. A systematic review of ODX use across 21 studies and 4,156 patients found that the mean proportion classified as low, intermediate, and high risk was 48.8, 39.0, and 12.2 % [19]. As in prior studies, the proportion of high-risk patients in this study was lower than that reported from the early validation study (8.4 vs. 27 %), suggesting that physicians are unlikely to recommend the test for patients who are at high risk based on clinical and pathologic characteristics, and reserve use of the test for patients at intermediate risk [3, 20].

Results of the analysis of ACT receipt were similar to prior studies that demonstrated that GEP assay results tend to change provider treatment decisions [15]. Among patients who did not receive the assay, approximately 15 % received ACT. Only 7 % of patients in our population determined to be low risk by the assay (more than half of the patients) received ACT, but 32 % of intermediate-risk and 63 % of high-risk patients were treated. A systematic review of 14 studies reported that the proportion of low-, intermediate-, and high-risk patients receiving ACT was 5.8, 37.4, and 83.4 %, respectively [19]. A recent study that utilized data from five registries linked to both health claims data and ODX data reported that among women under age 65, the proportion of low-, intermediate-, and high-risk patients receiving chemotherapy was 11, 47, and 88 %, respectively [21]. Nearly 96 % of high-risk patients in the SEER Patterns of Care study that supplemented registry data with additional treatment information from medical records received ACT [11]. It is likely that ACT, often administered in outpatient settings, was underreported to the CCR. An NCI study that compared SEER treatment data with treatment from Medicare claims reported that SEER registries captured about 69 % of chemotherapy treatment for breast cancer patients [22].

Limitations of this study are those common to cancer registry-based studies. Clinical information was limited, and, in particular, information was unavailable about factors that contributed to patient and provider decisions about testing and treatment. Likewise, information on patient comorbidities that may have influenced patient and provider decisions about treatment was not available. We only evaluated utilization of the ODX assay and cannot comment on utilization of other GEP assays, but ODX was by far the most commonly used GEP assay during this period.

In conclusion, the results of this study of over 23,000 breast cancer patients in California, diverse in age, race/ethnicity, and socioeconomic status, suggest that utilization of GEP among eligible breast cancer patients was quite low in California during the study period. The low utilization of this test suggests that some patients and providers lacked

confidence in and were unwilling to make treatment decisions based on GEP during the period covered by this study. Further research is needed to identify barriers to testing. A recently published and widely reported prospective trial followed over 1,600 women with a low recurrence score who received hormone therapy but not ACT. These patients experienced a 98 % overall survival rate, and 99 % were free of distant recurrence at 5 years [23]. Results of this and similar studies will likely increase awareness of and use of the GEP to improve care for cancer patients.

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