



Impact of Genomic Assay Testing and Clinical Factors on Chemotherapy Use After Implementation of Standardized Testing Criteria

Citation

Natsuhara, Kelsey H. 2018. Impact of Genomic Assay Testing and Clinical Factors on Chemotherapy Use After Implementation of Standardized Testing Criteria. Doctoral dissertation, Harvard Medical School.

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**Scholarly Report submitted in partial fulfillment of the MD Degree at
Harvard Medical School**

Date: 15 February 2018

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Scholarly Report Title: Impact of genomic assay testing and clinical factors on chemotherapy use after implementation of standardized testing criteria

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ABSTRACT

Title: Impact of genomic assay testing and clinical factors on chemotherapy use after implementation of standardized testing criteria

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Purpose: For clinically appropriate early-stage breast cancer patients, reflex criteria for Oncotype DX ordering (“the intervention”) was implemented at our comprehensive cancer center, which reduced time-to-adjuvant chemotherapy initiation. Our objective was to evaluate Oncotype DX ordering practices and chemotherapy use pre- and post-intervention.

Methods: We examined medical records for 498 patients who had definitive breast cancer surgery at our center. The post-intervention cohort consisted of 232 consecutive patients who had Oncotype DX testing after reflex criteria implementation and were compared to a retrospective cohort of 266 patients, including those who did and did not have Oncotype DX ordered before reflex criteria implementation. Factors associated with Oncotype DX ordering pre- and post-intervention were examined. We used multivariate logistic regression to evaluate factors associated with chemotherapy receipt among patients with Oncotype DX testing.

Results: The distribution of Oncotype DX scores, the proportion of those having Oncotype DX testing (28.9% vs. 34.1%) and those receiving chemotherapy (14.3% vs 19.4%) did not significantly change between pre- and post-intervention. Age ≤ 65 years, stage II, grade II, 1-3+ nodes, and tumor size $>2\text{cm}$ were associated with higher odds of Oncotype DX testing. Among patients having Oncotype DX testing, node status and Oncotype DX scores were significantly associated with chemotherapy receipt.

Conclusion: Our criteria for reflex Oncotype DX ordering appropriately targeted patients for whom Oncotype DX would typically be ordered by providers. No significant change in the rate of Oncotype DX ordering or chemotherapy use was observed after reflex testing implementation.

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Glossary of Abbreviations

AC	Doxorubicin + cyclophosphamide
ACT	Doxorubicin + cyclophosphamide + paclitaxel
AJCC	American Joint Committee on Cancer
CI	Confidence intervals
DF/BWCC	Dana-Farber/Brigham and Women's Cancer Center
ER	Estrogen receptor-positive
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
LVI	Lymphovascular invasion
NCI	National Cancer Institute
OR	Odds ratios
PR	Progesterone receptor
TC	Docetaxel + cyclophosphamide

Description of Student Contributions

My Scholars in Medicine project is entitled “Impact of genomic assay testing and clinical factors on chemotherapy use after implementation of standardized testing criteria.” I worked on this project with Dr. Rachel Freedman and Senior Project Manager, Katya Losk, from October 2015 through January 2018.

At the onset of the project, I met with Dr. Freedman and Ms. Losk to discuss a quality improvement project at the Dana-Farber Cancer Institute in the Breast Oncology Group to implement reflex criteria for Oncotype DX ordering. Dr. Freedman and Ms. Losk were interested in studying how this intervention might change practice patterns at this institution. Dr. Freedman and Ms. Losk were able to provide a patient dataset that required retrospective chart-review to complete the study. Together, we developed a database, discussed what data variables we wanted to collect for each patient, and reviewed inclusion and exclusion criteria for the study. I performed all chart review for over 500 patients (some excluded from the final analysis) in the pre-intervention and post-intervention cohorts. This chart review was conducted over approximately 18 months.

Next, I worked with Dr. Freedman and Ms. Losk to clean and review the data. Together we discussed and developed a plan for statistical analyses. I had the help of a statistician, Kristen Camuso, to perform the data analysis and worked with her to ensure the analyses were performed correctly. Dr. Freedman, Ms. Losk, and I met on a frequent basis to then discuss the results of the data and outline a plan to write up the project.

I performed an independent literature review and drafted the initial manuscript. I also created the tables and figures for the paper. Then, under the mentorship of Dr. Freedman and Ms. Losk, I edited and refined the manuscript. We circulated it among the remaining co-authors and I fielded and incorporated their edits. Some of this time, I was working part-time in between core rotations in the hospital. I was also able to work on the project full-time for two months in the summer of 2017 to complete the data collection and begin statistical analysis and manuscript writing. The manuscript has been submitted to a journal and we are awaiting their decision. The submitted manuscript is attached in this report.

APPENDIX: Manuscript

INTRODUCTION

The advent of genomic assays has allowed for a more personalized approach to breast cancer treatment. Oncotype DX (Genomic Health, Inc., Redwood City, CA) is a 21-gene assay that provides a 10-year estimate for the risk of distant breast cancer recurrence and the benefit of chemotherapy for patients with early-stage hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer (1). Oncotype DX is widely utilized by oncologists to assist in adjuvant treatment decisions and is included in all major breast cancer clinical guidelines (2-5). It was also recently incorporated in the 8th edition of the American Joint Committee on Cancer (AJCC) Breast Cancer Staging Manual (6). This is the first time a genomic platform has been included in a staging system, presenting new challenges for providers to obtain and utilize this information in an efficient and effective manner. Incorporating Oncotype DX testing into clinical practice has been shown to limit unnecessary chemotherapy use, leading to decreased patient morbidity, and reduced health care costs (7-9). However, additional testing frequently introduces delays into treatment decision-making and chemotherapy initiation (10-14).

At the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC), reflex Oncotype DX ordering criteria were developed through a multidisciplinary consensus process with input from medical oncologists, breast surgeons, and pathologists with the goal of identifying patients for whom the majority of clinicians would typically consider Oncotype DX testing to inform chemotherapy decisions. The goal of this "intervention" was to reduce treatment delays by having breast surgeons order the test immediately after the post-operative pathology results are available for patients ≤ 65 years of age with HR+/HER2- tumors who meet certain pathologic criteria: T1cN0 (grade II-III), T2N0 (grade I-II), or T1/T2N1 (grade I-II) disease. In prior work, we found that this intervention significantly decreased both the time in receiving Oncotype DX results post-operatively and the time from surgery to chemotherapy initiation by over one week (15).

Understanding which patients are most likely to benefit from Oncotype DX testing is paramount in balancing the test's benefits of reducing morbidity from unwarranted chemotherapy with the increased costs and delays that additional testing introduces into the breast cancer treatment

timeline. However, the impact of reflex ordering criteria on Oncotype DX ordering practices and receipt of chemotherapy has not been widely studied. In this study, we examined whether our Oncotype DX reflex ordering criteria appropriately captures similar patient populations before and after intervention implementation and the impact on chemotherapy use. We evaluated Oncotype DX ordering practices and chemotherapy receipt pre- and post-implementation of reflex criteria in order to explore whether reflex testing contributes to over- or under-testing, to better understand how testing influences treatment decisions, and to inform further refinement of our reflex criteria.

MATERIALS AND METHODS

Research Setting and Data Sources

DF/BWCC is a National Cancer Institute (NCI)-designated comprehensive cancer center with over 4,000 unique new breast cancer patients annually. Our center employs a multidisciplinary clinic model where the vast majority of patients with early-stage invasive breast cancer are seen at initial consultation by both a medical and surgical oncologist. Patient socio-demographic, clinical characteristics and adjuvant chemotherapy regimens were obtained through manual retrospective chart review and data extraction from clinical information systems. Oncotype DX recurrence scores were obtained from Genomic Health for the time period studied. Reflex ordering for Oncotype DX was implemented in January 2016, as described above. Patients >65 years of age were excluded from the reflex criteria for two main reasons: 1) to avoid unnecessary over-testing given the somewhat different risk-benefit considerations in older women when considering adjuvant chemotherapy, and 2) given issues with coverage and reimbursement in the immediate (14-day) post-operative period among patients insured by Medicare. Medical oncologists could also elect to order Oncotype DX testing on any patient with characteristics outside of reflex criteria.

Because this study was a retrospective medical record review, it was determined to be exempt from review by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Patient Cohorts

Female patients with HR+ (estrogen receptor-positive [ER+] or progesterone receptor-positive [PR+]) and HER2- breast cancer were eligible for study inclusion. During the post-intervention period (February-November 2016), we identified 242 consecutive patients who had Oncotype DX

ordered following definitive breast surgery. Overall, 10 patients were excluded for unilateral or bilateral primary breast cancer of mixed subtypes (HER2+/-), neoadjuvant therapy, medical oncology follow-up at an outside hospital, if their current diagnosis was a localized recurrence within 3 years of initial diagnosis, or for an erroneous order of Oncotype DX. The final “post-intervention cohort” included 232 patients. During the post-intervention period, a total of 680 patients with HR+/HER2- breast cancer underwent surgery, serving as the denominator to calculate the percent of patients who underwent Oncotype DX testing during this time period.

We compared the post-intervention cohort to a retrospective cohort of patients treated at our center prior to reflex Oncotype DX ordering. This “pre-intervention” cohort consisted of 366 consecutive women who underwent definitive breast cancer surgery between October 2014 and March 2015 and included both patients who had Oncotype DX ordered and those who did not. The faculty at our center was consistent during the time period studied. One-hundred patients were excluded for stage 0 cancer, receipt of neoadjuvant therapy, medical oncology follow-up at an outside hospital, a simultaneous second primary cancer, or if their current diagnosis was a localized recurrence within 3 years of initial diagnosis. Thus, 266 patients were included in the pre-intervention analytic cohort: 77 with Oncotype DX ordered and 189 without. Full inclusion and exclusion criteria for the pre- and post-intervention cohorts are detailed in **Figure 1**.

Outcomes of Interest

Our primary outcomes of interest were Oncotype DX ordering (yes/no) and chemotherapy receipt (yes/no). Chemotherapy receipt was defined as having any standard of care chemotherapy regimen in the adjuvant setting, ascertained through medical record abstraction. Specific chemotherapy regimens were also captured.

Control Variables of Interest

Covariates of interest were those clinically relevant to treatment decisions and differed for each outcome examined, including age at the time of surgery (<50, 50-65, >65 years), insurance (private vs public), race (white vs non-white), AJCC 7th edition stage (I, II, III) (16), grade (I, II, III), nodal status (0, 1-3, >3 positive nodes), single vs multifocal tumor, lymphovascular invasion (LVI; none, single focus, multiple), tumor size (≤ 2 cm vs > 2 cm), surgery type (lumpectomy vs mastectomy), and Oncotype DX recurrence score (low < 18 , intermediate 18-30, high > 30).

Statistical Analysis

We compared patient demographics and tumor characteristics for patients with and without Oncotype DX testing using Chi-square analyses. The percentage of patients who received Oncotype DX testing pre- and post-intervention cohorts was also compared using Chi-square testing. We then performed a multivariate logistic regression model to examine factors associated with chemotherapy use, including age, insurance type, race, grade, nodal status, multifocal tumors, LVI, tumor size, and Oncotype DX recurrence score, and time period (pre vs post intervention). Because stage was redundant with tumor size and nodal status and was not independently associated with outcomes, it was not included in the multivariate model. Patients whose nodal status was unknown were excluded from the model (n=34). Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and p-values were calculated to ascertain the strength of association between each variable and receipt of chemotherapy. All analyses were conducted using SAS Version 9.4.

RESULTS

Characteristics of Patients with and without Oncotype DX Ordered

The pre-intervention cohort included 266 patients treated at our center prior to reflex criteria implementation. In this group, 28.9% (n=77) had Oncotype DX ordered and 71.1% (n=189) did not (**Figure 1**). The post-intervention cohort included 232 patients who underwent Oncotype DX testing, among the 680 patients with HR+/HER2- cancers who were most appropriate for Oncotype DX testing (34.1% of patients). There was no statistical difference in the proportion of patients who had Oncotype DX testing in the pre- vs post-intervention settings (p=0.12). Among the post-intervention patients, 63.8% (n=148) met reflex criteria, while 36.2% (n=84) had testing ordered by their medical oncologist.

The differences in characteristics between patients who had Oncotype DX ordered compared to those who did not in the combined pre- and post-intervention cohorts are shown in **Table 1**. Age <50 years and 50-65 years (70.8% and 68.8% tested vs 41.2% in those age >65 years, p<0.0001) and private insurance (72.6% vs 35.5% tested, p<0.0001) were associated with Oncotype DX testing. Stage II tumors, grade II or III disease, tumors >2cm, and patients with 1-3 positive lymph

nodes were more likely to have Oncotype DX ordered ($p<0.001$). Race, single vs multifocal cancer, and LVI were not significantly associated with Oncotype DX ordering.

Factors Associated with Oncotype DX Ordering Pre- and Post-Intervention

Age (50-65 years), private insurance, and having a single focus of cancer were all significantly associated with increased Oncotype DX ordering in the post-intervention vs pre-intervention cohorts (**Table 2**). No significant difference in the distribution of Oncotype DX recurrence scores was observed between the pre- and post-intervention cohorts ($p=0.27$). Patient race, cancer stage, grade, nodal status, LVI, and tumor size were not associated with a significant change in Oncotype DX ordering between pre- and post-intervention cohorts.

Factors Associated with Chemotherapy Receipt after Oncotype DX Testing

The multivariate analysis in **Table 3** highlights factors associated with adjuvant chemotherapy receipt among all patients who had Oncotype DX ordered. Among the 309 patients with Oncotype DX ordered, 56 (18.1%) received adjuvant chemotherapy, including 11 (14.3%) patients from the pre-intervention cohort and 45 (19.4%) patients from the post-intervention cohort ($p=0.31$). Patients with node-positive disease (OR=3.72, 95% CI=1.58-8.77) and intermediate (18-30) and high (>30) Oncotype DX recurrence scores (OR=16.48, 95% CI=6.27-43.30; OR=97.46, 95% CI=18.36-517.37) were significantly more likely to receive chemotherapy. No difference was observed in the proportion of patients who received chemotherapy in the pre- or post-intervention settings ($p=0.31$). Additionally, in the pre-intervention cohort, 16.9% of patients who did not have Oncotype DX ordered received chemotherapy (**Figure 1**). Of note, 72.8% of patients overall with positive lymph nodes and 61.0% with grade III cancers did not receive chemotherapy.

Among the 11 pre-intervention patients who received chemotherapy after Oncotype DX ordering, 54.5% (n=6) received doxorubicin + cyclophosphamide (AC), 27.3% (n=3) received docetaxel + cyclophosphamide (TC), and 18.2% (n=2) received doxorubicin + cyclophosphamide + paclitaxel (ACT). Among the 45 post-intervention patients who received chemotherapy after Oncotype DX ordering, 17.8% (n=8) received AC, 44.4% (n=20) received TC, 33.3% (n=15) received ACT, and 4.4% (n=2) received an alternate regimen.*

*Cyclophosphamide+methotrexate+5-FU (n=1) and carboplatin + paclitaxel (n=1)

DISCUSSION

In this contemporary analysis of 498 patients in a single, high-volume comprehensive cancer center, we examined factors associated with Oncotype DX ordering and adjuvant chemotherapy administration before and after implementation of reflex criteria for Oncotype DX testing. Because of our pre-specified reflex criteria, patients ≤ 65 years of age and those with private insurance were more likely to have Oncotype DX ordered post-intervention vs pre-intervention. Interestingly, among those having Oncotype DX testing, recurrence score was the factor most significantly associated with chemotherapy use, indicating that once this test is sent, it is often the deciding factor in chemotherapy decisions over any other patient or tumor variable. This is consistent with a recent large, prospective study in the Netherlands that demonstrated the use of gene expression profiling changed chemotherapy treatment decisions in 51% of patients who underwent testing (17). Our results further confirm the utility of reflex criteria testing; as we previously established that this intervention results in shorter times to chemotherapy initiation for those receiving treatment (15) and our current work presented here, demonstrates the importance of genomic assay testing in chemotherapy decision-making, with most women being spared chemotherapy.

Reassuringly, similar proportions of patients received adjuvant chemotherapy before and after the intervention. These results demonstrate that our multidisciplinary consensus criteria for Oncotype DX ordering are reflective of our center's clinical practice, appropriately capturing the patient population for whom oncologists would have otherwise ordered Oncotype DX testing, but doing so faster. This will be particularly important as Oncotype DX becomes increasingly pivotal in cancer staging (6). Moreover, the percentage of patients who received Oncotype DX testing before and after implementation of reflex criteria was not significantly different, demonstrating that use of reflex criteria did not lead to over-usage of testing. Rather, our findings suggest that the selected testing criteria aided clinicians in more efficiently providing care that reflects their clinical judgment. A recent study at a NCI designated cancer center also found that implementing guideline-directed early Oncotype DX ordering maintained a stable chemotherapy rate, and found that overall patient costs were not appreciably different before and after their intervention, further supporting that reflex criteria are an effective method to streamline Oncotype DX ordering (18).

Of note, the chemotherapy rate observed in patients with Oncotype DX testing was lower in our study vs previously published reports (3, 19). This likely represents an evolving practice away from chemotherapy use for most patients with HR+/HER2- disease, as comfort with Oncotype DX testing improves and the benefits of chemotherapy are increasingly felt to be limited to a small proportion of these patients. An example of this was observed in our model of chemotherapy receipt. Though positive nodal status was significantly associated with receiving adjuvant chemotherapy, 72.8% of patients with node-positive disease who had Oncotype DX ordered did not receive chemotherapy. This suggests that Oncotype DX may also be a valuable tool in sparing many lymph node-positive patients from chemotherapy, as suggested by some guidelines (20). Clinical practice will be informed by the forthcoming results of the “RxPONDER” trial (Rx for Positive Node, Endocrine Responsive Breast Cancer; NCT01272037), which seeks to prospectively evaluate the utility of Oncotype DX testing in node-positive disease and the benefits of chemotherapy.

Prior studies have also attempted to target the patients most likely to benefit from Oncotype DX testing using clinical and demographic criteria (21-24). Kim *et al.* developed a model that predicted Oncotype DX risk category in 52.5% of cases and then modeled how ordering practices might change after broad implementation of their prediction strategy (21). They projected that, if widely implemented, their risk prediction model could identify a group of patients for whom Oncotype DX ordering was likely to contribute information beyond standard clinico-pathologic data. However, there is very little literature studying the outcome of implementing such prediction strategies into clinical practice and we are unaware of any literature that has evaluated the criteria used for reflex or early testing strategies.

Through our study, we identified potential ways to revise reflex criteria for Oncotype DX ordering in our practice. When comparing patients who had Oncotype DX testing pre- and post-intervention, patients with multifocal cancers were more likely to have Oncotype DX ordered post-intervention, a factor not addressed by reflex criteria; thus, highlighting a variable that providers found important in treatment decisions and a possible area where reflex criteria could be broadened. In addition, among patients with grade III cancers who underwent Oncotype DX testing, 61.0% did not receive chemotherapy. Increasing the use of reflex testing in the setting of

high grade cancers (where the majority will have low or intermediate scores (25)) is an area of active discussion within our center.

We recognize several limitations to this study. First, this was a single center, retrospective study and we acknowledge that practice patterns may not be widely generalizable. However, we feel that implementation of reflex testing and its outcomes thus far are of larger interest and could have broader implications if the time to chemotherapy initiation could be influenced on a wider scale. Second, because the number of patients receiving chemotherapy was low, despite a large sample size, results for some subgroups yielded wide confidence intervals and some categories were collapsed, such as grade because of small sample sizes. However, the factors that were significant, such as high Oncotype DX recurrence scores, had markedly positive ORs, still providing valuable information regarding the role of these variables in chemotherapy initiation. Third, we could not ascertain whether recurrence and survival rates changed between the pre- and post-intervention cohorts and/or if chemotherapy was administered appropriately, due to the short follow-up times available with our recent implementation of the reflex ordering process; though, we will examine this in future studies.

Despite these limitations, we demonstrated that implementing multidisciplinary consensus reflex criteria for Oncotype DX ordering maintains a stable Oncotype DX ordering rate and chemotherapy rate, mirroring what we observe in our specific clinical practice, while decreasing treatment delays due to additional testing (15). Our reflex criteria appropriately capture a population of women who would likely have had Oncotype DX ordered by their providers and for whom the results of this test are predicted to influence management. This intervention serves as a potential model for other large integrated, multidisciplinary oncology centers to implement institutional processes to target the patient population most likely to benefit from genomic assay testing, while mitigating treatment-delays.

Acknowledgments: We thank all of the patients who contributed to our database.

Research Support: This study was supported by the following: Dr. Freedman is supported by the American Cancer Society (125912-MRSG-14-240-01-CPPB) and Susan G. Komen (CCR CCR14298143).

REFERENCES

1. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *The New England journal of medicine*. 2004;351(27):2817-26. doi: 10.1056/NEJMoa041588. PubMed PMID: 15591335.
2. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2016;14(3):324-54. Epub 2016/03/10. PubMed PMID: 26957618.
3. Hassett MJ, Silver SM, Hughes ME, Blayney DW, Edge SB, Herman JG, et al. Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(18):2218-26. doi: 10.1200/JCO.2011.38.5740. PubMed PMID: 22585699; PubMed Central PMCID: PMC3397718.
4. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2015;26 Suppl 5:v8-30. Epub 2015/09/01. doi: 10.1093/annonc/mdv298. PubMed PMID: 26314782.
5. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25(33):5287-312. Epub 2007/10/24. doi: 10.1200/jco.2007.14.2364. PubMed PMID: 17954709.
6. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging

manual. *CA Cancer J Clin.* 2017;67(4):290-303. doi: 10.3322/caac.21393. PubMed PMID: 28294295.

7. Kip M, Monteban H, Steuten L. Long-term cost-effectiveness of Oncotype DX(R) versus current clinical practice from a Dutch cost perspective. *J Comp Eff Res.* 2015;4(5):433-45. doi: 10.2217/ce.15.18. PubMed PMID: 25872415.

8. Henry NL, Somerfield MR, Krop IE. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations Summary. *J Oncol Pract.* 2016;12(5):482-4. doi: 10.1200/JOP.2016.011205. PubMed PMID: 27006356.

9. Katz G, Romano O, Foa C, Vataire AL, Chantelard JV, Herve R, et al. Economic Impact of Gene Expression Profiling in Patients with Early-Stage Breast Cancer in France. *PloS one.* 2015;10(6):e0128880. doi: 10.1371/journal.pone.0128880. PubMed PMID: 26086912; PubMed Central PMCID: PMC4472722.

10. Losk K, Vaz-Luis I, Camuso K, Batista R, Lloyd M, Tukenmez M, et al. Factors Associated With Delays in Chemotherapy Initiation Among Patients With Breast Cancer at a Comprehensive Cancer Center. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2016;14(12):1519-26. Epub 2016/12/14. PubMed PMID: 27956536.

11. Liederbach E, Sisco M, Wang C, Pesce C, Sharpe S, Winchester DJ, et al. Wait times for breast surgical operations, 2003-2011: a report from the National Cancer Data Base. *Annals of surgical oncology.* 2015;22(3):899-907. Epub 2014/09/23. doi: 10.1245/s10434-014-4086-7. PubMed PMID: 25234018.

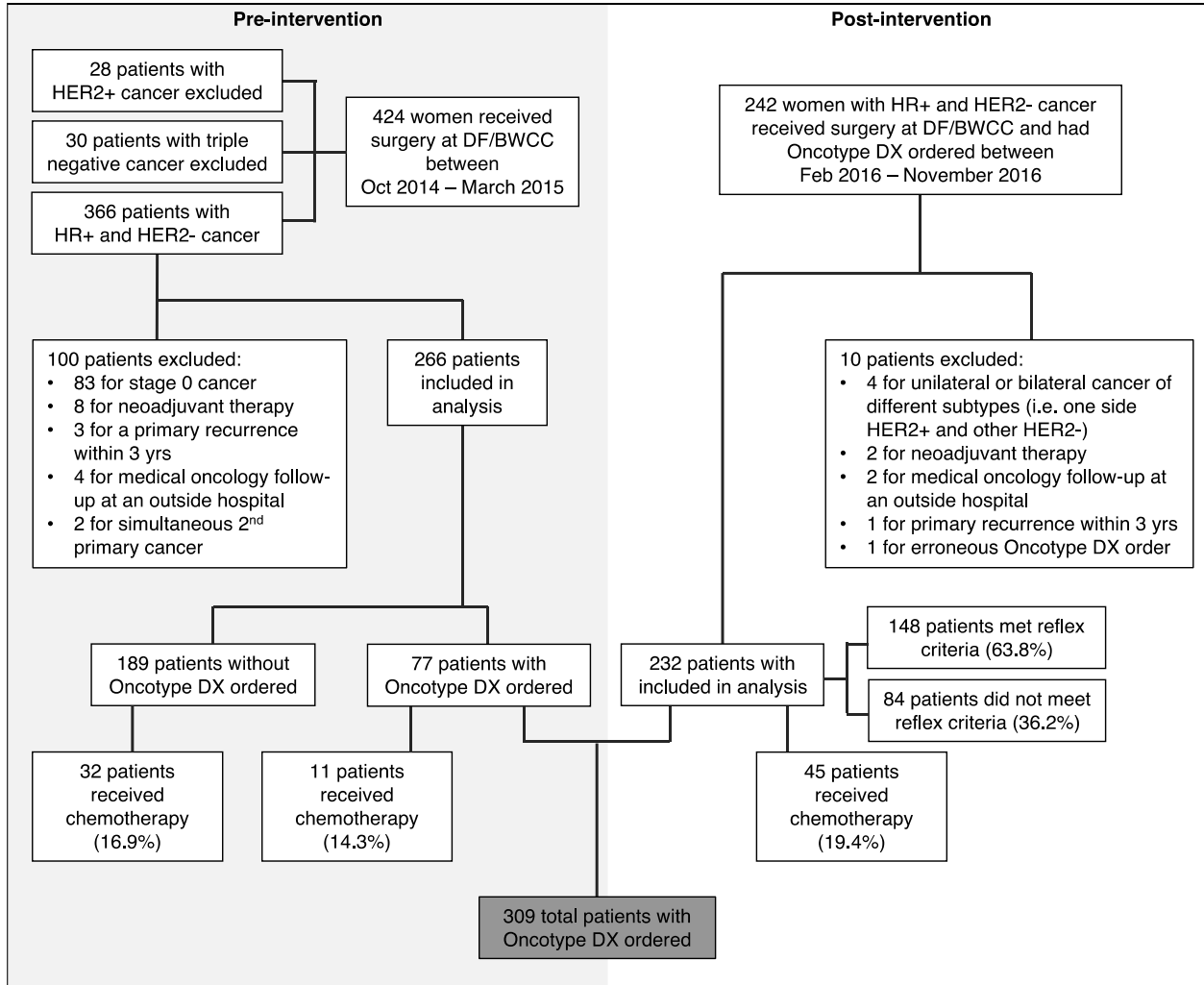
12. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong YN, et al. Time to Surgery and Breast Cancer Survival in the United States. *JAMA oncology*. 2016;2(3):330-9. Epub 2015/12/15. doi: 10.1001/jamaoncol.2015.4508. PubMed PMID: 26659430; PubMed Central PMCID: PMC4788555.
13. Saint-Jacques N, Younis T, Dewar R, Rayson D. Wait times for breast cancer care. *British journal of cancer*. 2007;96(1):162-8. Epub 2006/12/21. doi: 10.1038/sj.bjc.6603523. PubMed PMID: 17179986; PubMed Central PMCID: PMC2360218.
14. Vandergrift JL, Niland JC, Theriault RL, Edge SB, Wong YN, Loftus LS, et al. Time to adjuvant chemotherapy for breast cancer in National Comprehensive Cancer Network institutions. *Journal of the National Cancer Institute*. 2013;105(2):104-12. Epub 2012/12/25. doi: 10.1093/jnci/djs506. PubMed PMID: 23264681; PubMed Central PMCID: PMC3611850.
15. Losk K, Freedman RA, Lin NU, Golshan M, Pochebit SM, Lester SC, et al. Implementation of Surgeon-Initiated Gene Expression Profile Testing (Onco type DX) Among Patients With Early-Stage Breast Cancer to Reduce Delays in Chemotherapy Initiation. *J Oncol Pract*. 2017;13(9):e815-e20. doi: 10.1200/JOP.2017.023788. PubMed PMID: 28858535.
16. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology*. 2010;17(6):1471-4. doi: 10.1245/s10434-010-0985-4. PubMed PMID: 20180029.
17. Kuijer A, Straver M, den Dekker B, van Bommel ACM, Elias SG, Smorenburg CH, et al. Impact of 70-Gene Signature Use on Adjuvant Chemotherapy Decisions in Patients With Estrogen Receptor-Positive Early Breast Cancer: Results of a Prospective Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(24):2814-9. doi: 10.1200/JCO.2016.70.3959. PubMed PMID: 28813638.

18. Dzimitrowicz H, Mougalian S, Storms S, Hurd S, Chagpar AB, Killelea BK, et al. Impacts of Early Guideline-Directed 21-Gene Recurrence Score Testing on Adjuvant Therapy Decision Making. *J Oncol Pract*. 2017;JOP2017022731. doi: 10.1200/JOP.2017.022731. PubMed PMID: 29048991.
19. Friese CR, Li Y, Bondarenko I, Hofer TP, Ward KC, Hamilton AS, et al. Chemotherapy decisions and patient experience with the recurrence score assay for early-stage breast cancer. *Cancer*. 2017;123(1):43-51. doi: 10.1002/cncr.30324. PubMed PMID: 27775837; PubMed Central PMCID: PMC5161570.
20. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Breast Cancer (Version 3.2017) [Jan 25, 2018]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
21. Kim HS, Umbricht CB, Illei PB, Cimino-Mathews A, Cho S, Chowdhury N, et al. Optimizing the Use of Gene Expression Profiling in Early-Stage Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34(36):4390-7. Epub 2016/12/22. doi: 10.1200/jco.2016.67.7195. PubMed PMID: 27998227; PubMed Central PMCID: PMC5455310.
22. Turner BM, Skinner KA, Tang P, Jackson MC, Soukiazian N, Shayne M, et al. Use of modified Magee equations and histologic criteria to predict the Oncotype DX recurrence score. *Mod Pathol*. 2015;28(7):921-31. doi: 10.1038/modpathol.2015.50. PubMed PMID: 25932962.
23. Gage MM, Rosman M, Mylander WC, Giblin E, Kim HS, Cope L, et al. A Validated Model for Identifying Patients Unlikely to Benefit From the 21-Gene Recurrence Score Assay. *Clin Breast Cancer*. 2015;15(6):467-72. doi: 10.1016/j.clbc.2015.04.006. PubMed PMID: 26072275; PubMed Central PMCID: PMC54847530.

24. Klein ME, Dabbs DJ, Shuai Y, Brufsky AM, Jankowitz R, Puhalla SL, et al. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. *Mod Pathol.* 2013;26(5):658-64. doi: 10.1038/modpathol.2013.36. PubMed PMID: 23503643; PubMed Central PMCID: PMC3647116.
25. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(23):3726-34. Epub 2006/05/25. doi: 10.1200/jco.2005.04.7985. PubMed PMID: 16720680.

Figures and Tables

Figure 1: Inclusion and Exclusion Criteria



Key: DF/BWCC = Dana-Farber/Brigham and Women's Cancer Center; HER2 = human epidermal growth factor-2; HR = hormone receptor

Table 1: Characteristics of patients with and without Oncotype DX ordered (n=498)^a

	Oncotype DX ordered (n=309), n (%)	Oncotype DX not ordered (n=189), n (%)	p-value ^b
Age			
<50	85 (70.8)	35 (29.2)	<0.0001*
50-65	170 (68.8)	77 (31.2)	
>65	54 (41.2)	77 (58.8)	
Insurance			
Private	259 (72.6)	98 (27.4)	<0.0001*
Public	50 (35.5)	91 (64.5)	
Race			
White	271 (64.1)	152 (35.9)	0.03*
Non-White	38 (50.7)	37 (49.3)	
Stage (n=464)^c			
I	150 (55.4)	121 (44.6)	<0.0001*
II	140 (84.3)	26 (15.7)	
III	8 (29.6)	19 (70.4)	
Grade			
I	40 (39.2)	62 (59.6)	<0.0001*
II	210 (68.6)	96 (31.4)	
III	59 (65.6)	31 (34.4)	
Node Positivity (n=464)^c			
0	206 (61.3)	130 (38.7)	<0.0001*
1-3	89 (77.4)	26 (22.6)	
>3	3 (23.1)	10 (76.9)	
Multifocal			
Single	204 (59.5)	139 (40.5)	0.08
Multifocal	105 (67.7)	50 (32.3)	
LVI			
None	214 (59.3)	147 (40.7)	0.13
Single Focus	22 (62.9)	13 (37.1)	
Multiple Foci	71 (70.3)	30 (29.7)	
Tumor Size			
≤2 cm	209 (57.6)	154 (42.4)	0.0007*
>2 cm	100 (74.1)	35 (25.9)	
Surgery Type			
Lumpectomy	124 (49.6)	126 (50.4)	0.38
Mastectomy	68 (51.9)	63 (48.1)	

Key: LVI: lymphovascular invasion

*Statistically significant (p-val<0.05)

^a Patients without Oncotype DX ordered are from the pre-intervention cohort only. Patients with Oncotype DX ordered are combined from pre- and post-intervention cohorts.^b p-values generated from Chi-square analyses.^c Node status and stage was unknown for 34 women.

Table 2: Characteristics of all patients with Oncotype DX ordered pre- and post-intervention (n=309)

	Pre-Intervention (n=77), n (%)	Post-Intervention (n=232), n (%)	p-value ^a
Age			
<50	15 (17.6)	70 (82.4)	0.04*
50-65	42 (24.7)	128 (75.3)	
>65	20 (37.0)	34 (63.0)	
Insurance			
Private	48 (18.5)	211 (81.5)	<0.0001*
Public	29 (58.0)	21 (42.0)	
Race			
White	63 (23.2)	208 (76.8)	0.07
Non-White	14 (36.8)	24 (63.2)	
Stage (n=298)^b			
I	37 (24.7)	113 (75.3)	0.27
II	35 (25.0)	105 (75.0)	
III	4 (50.0)	4 (50.0)	
Grade			
I	11 (27.5)	29 (72.5)	0.44
II	48 (22.9)	162 (77.1)	
III	18 (30.5)	41 (69.5)	
Node Status (n=298)^b			
Positive	26 (28.3)	66 (71.7)	0.46
Negative	50 (24.3)	156 (75.7)	
Multifocal			
Single	61 (29.9)	143 (70.1)	0.005*
Multifocal	16 (15.2)	89 (84.8)	
LVI			
None	53 (24.6)	162 (75.4)	0.81
Single Focus	7 (30.4)	16 (69.6)	
Multiple Foci	17 (23.9)	54 (76.1)	
Tumor Size			
≤2 cm	52 (24.6)	157 (75.1)	0.98
>2 cm	25 (25.0)	75 (75.0)	
Oncotype DX Score			
Low (<18)	51 (27)	138 (73.0)	0.27
Intermediate (18-30)	24 (23.8)	77 (76.2)	
High (>30)	2 (10.5)	17 (89.5)	
Surgery Type			
Lumpectomy	54 (27.8)	140 (72.2)	0.12
Mastectomy	23 (20.0)	92 (80.0)	

Key: LVI: lymphovascular invasion

* Statistically significant (p-val<0.05)

^a p-values generated from Chi-square analyses.

^b 34 women did not undergo axillary lymph node dissection, so node positivity and stage are unknown.

Table 3: Multivariate logistic regression evaluating factors associated with chemotherapy receipt after Oncotype DX testing (n=298)^a

	Received chemo (n=56), n (%)	Did not receive chemo (n=253), n (%)	Adjusted OR (95% CI)	p-value ^b
Age				
<50	18 (21.2)	67 (78.8)	1.00	0.62
50-65	30 (17.7)	140 (82.3)	1.05 (0.43-2.57)	
>65	8 (14.8)	46 (85.2)	0.59 (0.13-2.69)	
Insurance				
Private	50 (19.3)	209 (80.7)	1.00	0.22
Public	6 (12.0)	44 (88.0)	0.49 (0.12-2.04)	
Race				
White	51 (18.8)	220 (81.2)	2.17 (0.63-7.42)	0.40
Non-White	5 (13.2)	33 (86.8)	1.00	
Grade				
I-II	33 (13.2)	217 (86.8)	1.00	<0.0001*
III	23 (39.0)	36 (61.0)	1.53 (0.59-3.99)	
Node Status (n=298)^a				
Positive	25 (27.7)	67 (72.8)	3.72 (1.58-8.77)*	0.007*
Negative	29 (14.1)	177 (85.9)	1.00	
Multifocal				
Single	38 (18.6)	166 (81.4)	1.00	0.75
Multifocal	18 (17.1)	87 (82.9)	1.35 (0.58-3.13)	
LVI				
None	31 (14.4)	184 (85.6)	1.00	0.02*
Single Focus	4 (17.4)	19 (82.6)	0.71 (0.16-3.10)	
Multiple Foci	21 (29.6)	50 (70.4)	1.35 (0.53-3.41)	
Tumor Size				
≤2 cm	31 (14.8)	178 (85.2)	1.00	0.03*
>2 cm	25 (25.0)	75 (75.0)	1.67 (0.73-3.81)	
Oncotype DX Score				
Low (<18)	7 (3.7)	182 (96.3)	1.00	<0.0001*
Intermediate (18-30)	35 (34.7)	66 (65.3)	16.48 (6.27-43.40)*	
High (>30)	14 (73.7)	5 (26.3)	97.46 (18.36-517.37)*	
Time Period				
Pre-Intervention	11 (14.3)	66 (85.7)	1.00	0.31
Post-Intervention	45 (19.4)	187 (80.6)	0.78 (0.30-2.01)	

Key: CI = Confidence Intervals; LVI = lymphovascular invasion; OR = Odds Ratio

*Statistically significant (p-val<0.05)

^a n=309 for Chi-square analyses. n=298 for multivariate model. Node status was unknown for 34 patients and thus were excluded from the model.

^b p-values generated from Chi-square analyses.