RACIAL VARIATION IN THE USE OF ONCOTYPE DX TESTING FOR WOMEN WITH BREAST CANCER

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ABSTRACT

Megan Clarke Roberts: Racial Variation in the Use of Oncotype DX Testing among Women with Breast Cancer
(Under the direction of Morris Weinberger)

Oncotype DX (ODX) is a tumor gene-profiling test that aids in adjuvant chemotherapy decision-making. While ODX has the potential to improve quality of care, <50% of eligible women receive it. If there is differential ODX testing by race, well-documented disparities in quality of cancer care may persist or worsen. Thus, we had three research objectives: (1) examine racial variation in ODX test uptake, (2) examine racial variation in subsequent adjuvant chemotherapy initiation, and (3) explore how oncologists use the test, identifying barriers and facilitators.

We used mixed methods to explore these objectives. We used data from the Carolina Breast Cancer Study Phase III (n=2,998), a population-based cohort study of women diagnosed with breast cancer in 2008-2014. We used modified Poisson regression to determine the associations between race and (1) ODX testing (stratified by node status), and (2) adjuvant chemotherapy initiation (stratified by ODX risk group). We also conducted semi-structured interviews with oncologists (n=15). Interview transcripts were double-coded using template analysis.

Overall, 42% of women (n=1468) had ODX testing. We found no racial disparities in the uptake of ODX testing among node negative patients. However, among node positive patients, Black patients were 46% less likely to receive testing than non-Black women after controlling for clinical factors (aRR: 0.54, 95%CI:0.35-0.84, p=0.006). Among women who underwent ODX testing (n=541), 54.2%, 37.5%, and 8.3% of women had low-, intermediate- and high-risk tumors, respectively. We did not observe racial variation in adjuvant chemotherapy initiation. Several themes emerged from our provider interviews, including organizational, interpersonal, and intrapersonal factors that influenced ODX testing.

Overall, we did not find racial disparities in ODX testing for node negative patients for whom the test is guideline-recommended and widely covered by insurers; however, our findings suggested

that a newer application of ODX testing for node positive breast cancer was accessed less often by Black than non-Black women. This finding indicates more guideline-concordant treatment, but also may signal slower diffusion of newer test-applications among Black patients. As treatment decision-making becomes increasingly targeted with the use of genetic technologies, it may be important to examine their use across racial subgroups during early adoption.

Dedicated to my mom and dad.

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Second, I must thank Stephanie Wheeler for whom I have been a graduate research assistant for the past three years and who was a co-chair for this dissertation work. When I came to UNC, I wanted to gain experience in racial disparities research in breast cancer: Stephanie provided me that opportunity and more. I can still recall how excited I was when Morris told me that Stephanie was looking for a graduate research assistant during the summer of 2012. Her study explored racial

disparities in endocrine therapy adherence among breast cancer patients. That research experience has launched my path towards a career in cancer health outcomes research. Because of my experiences working with Stephanie: (1) I gained qualitative methods training, (2) I started attending the cancer health outcomes breakfasts and met amazing cancer researchers both at UNC and beyond, (3) I became linked in with the Carolina Breast Cancer Study Phase III, (4) I was able to publish my first, first-authored manuscript, and (5) I had the research experiences necessary to receive the Cancer Control Education Program predoctoral fellowship and the Cancer Prevention Training Program postdoctoral fellowship at the National Cancer Institute. Over the years, I have learned so much from Stephanie. Not only have she given me numerous research opportunities, but also she has been an exceptional mentor. Stephanie has always offered me candid advice, and at the times when I really needed support, she was always there. Stephanie has set an example of what it means to be a young woman in academia---I admire how much she has accomplished and how well respected she is so early in her career. At the last conference I went to (AACR The Science of Cancer Disparities), a researcher walked by my poster, which presented some of this dissertation work. This researcher stopped when she saw Stephanie's name on the poster, and said "Oh! Stephanie Wheeler---I have read and I admire her work. She is doing some very important and interesting research!" I couldn't have agreed more. Thank you, Stephanie for being a mentor and advocate these past three years.

I have had the privilege of learning from not just Stephanie, but several other amazing female mentors at UNC. Stacie Dusetzina is another of those mentors who has served as a role model. She has gone above and beyond the call of duty in terms of my mentorship over the past two years. I really got to know Stacie well during the fall of 2013. During this time, Stephanie was on maternity leave, and without hesitation Stacie helped me during a critical time when I was trying to determine which dataset would ultimately be feasible for my dissertation research. Stacie helped make what would have been a very stressful time, manageable and helped me to move forward and develop contingency plans. I cannot express how reassuring it was to have a back up plan for data, and Stacie was integral in arranging this. Also during this time, I realized I would not be able to conduct one of my originally proposed specific aims; Stacie was generous with her time and offered to

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always shared his passion for science with me, and it is no accident that I am studying genetic technologies and cancer. From when I was young, my dad taught me to pursue my passions and to use research as a mechanism for better understanding the world. He has taught me that a person is measured, not by material goods or status, but by pursuing a passion and making a difference. He has sacrificed much so that I could have amazing educational opportunities, and I am grateful for that. My dad is an amazing person, father, researcher, teacher, and friend: Thanks, Dad.

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LIST OF ABBREVIATIONS

ODX	Oncotype DX test®, Genomic Health, Redwood City, California
CMS	Centers for Medicare and Medicaid Services
CBCS-III	Carolina Breast Cancer Study, Phase III
IOM	Institute of Medicine
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
ASCO	American Society of Clinical Oncology
NCCN	National Comprehensive Cancer Network
AJCC	American Joint Committee on Cancer
NC	North Carolina
Med Rec Abs	Medical record abstraction
Path	Pathology report abstraction
MA_VARS	Derived variables from CBCS-III data
SES	Socioeconomic Status
SWOG	Southwest Oncology Group
RxPONDER	Rx for Positive Node Endocrine Therapy Responsive Breast Cancer
TAILORx	Trial Assigning IndividuaLized Options for Treatment
aRR	Adjusted risk ratio
RR	Risk Ratio
PSU	Primary Sampling Unit
Df	degrees of freedom
HS	High school
N	Sample size

CHAPTER 1. ONCOTYPE DX TESTING IN WOMEN WITH BREAST CANCER: OVERVIEW

Specific Aims

Breast cancer remains the second leading cause of cancer death among women, and while the incidence of breast cancer is lower among Black women, their breast cancer mortality is 37% higher compared to white women.[1, 2] Transformative research and technology have improved the prognosis and treatment of breast cancer in the past decade. However, even when controlling for known differences in tumor biology, racial disparities in breast cancer care processes and outcomes continue to grow[3, 4], suggesting that this racial disparity can be partially explained by access to high quality cancer treatment.[5, 6] In 2004, a genomic innovation in breast cancer treatment, Oncotype DX® (ODX), became commercially available [7]. ODX uses tumor genetics to predict not only risk of recurrence, but also the benefit of chemotherapy among early-stage, estrogen receptor positive breast cancer patients.[7] [8, 9] ODX began to be included in clinical guidelines in 2007 and reimbursed by CMS in 2006. ODX can improve treatment decision-making by avoiding the costs and risks associated with adjuvant chemotherapy among women with low risk scores [10-13]. However, some evidence suggests that eligible Black patients are less likely to utilize ODX testing compared to white patients [14-16]. Reasons for these disparities and whether these disparities persist across diverse health care settings and insurers remain unclear. Furthermore, it is unknown whether ODX testing impacts chemotherapy use equally across racial subgroups. Genomic diffusion research suggests that organizational, provider, and patient level characteristics contribute to racial disparities in genetic testing uptake across diverse health care settings [17]. However, to my knowledge, no studies have explored racial disparities in ODX uptake and subsequent adjuvant chemotherapy initiation across a diversity of health care settings and insurance types.

The long-term goal of this research is to narrow racial disparities in breast cancer treatment and outcomes by developing interventions that increase access to genomic technologies, such as ODX testing, among minority cancer patients. The objective of this study is to identify whether racial

disparities exist in ODX test use and to identify modifiable factors that (1) contribute to racial disparities in ODX uptake and subsequent adjuvant chemotherapy initiation and (2) inform future interventions. The central hypothesis of this work is that Black women are less likely to receive ODX testing compared to white women and that ODX testing impacts chemotherapy behaviors differentially by racial subgroup. Literature has demonstrated that racial disparities in breast cancer care emerge not only due to access to innovative technologies, but also during the treatment decision-making process.[17] The rationale for this study is to close a gap in our current understanding of how race influences ODX uptake and adjuvant chemotherapy use across diverse health organizations in North Carolina. Identifying these factors will move the field forward by providing an evidence base to inform future interventions aimed at increasing patients' access to and the appropriate use of ODX testing and other genetic technologies among minority populations. This leads to the following three aims and hypotheses to be tested using Carolina Breast Cancer Study (CBCS-III), a unique and rich dataset that includes survey and medical record abstraction data for 2998 women across North Carolina, as well as interviews with oncologists in North Carolina:

Aim 1: **Determine whether ODX test use varies by racial subgroup.** *Hypothesis:* ODX testing is lower among Black patients compared to white patients. I will build multivariate regression models using CBCS-III data.

Aim 2: **Determine the independent and interactive effects of race with ODX risk score on the initiation of guideline-concordant adjuvant chemotherapy.** *Hypothesis 2a:* Black women will be less likely to receive guideline-concordant chemotherapy within the low and high-risk groups compared to white women. *Hypothesis 2b:* Black women will be less likely to initiate adjuvant chemotherapy within the intermediate risk group compared to white women. I will use CBCS-III data to elucidate the relationship between race and ODX risk score on adjuvant chemotherapy use among NC breast cancer patients.

Aim 3: **Identify the perceived organizational and provider barriers and facilitators among oncologists for recommending ODX, as well as how results are used in breast cancer care, among eligible women with breast cancer**. I will conduct semi-structured phone interviews with up to 20 oncologists sampled across a range of health care settings in NC.

As genomic technologies shift cancer treatment towards personalized therapies, it is critical to understand utilization patterns across patient populations and health care settings and to identify factors that can increase access to high quality cancer care for all patients. I seek to elucidate whether race influences the use of transformative genomic technologies, such as ODX testing (Aim 1). Furthermore, I expect to identify whether ODX risk score influences adjuvant chemotherapy initiation differentially by race (Aim 2). Qualitative interviews with oncologists across diverse settings will compliment current understanding of ODX use and subsequent treatment decision-making by focusing on factors that cannot be studied using secondary data sources (Aim 3). Taken as a whole, results from these three aims can inform future interventions and policies aimed to provide high quality care to all breast cancer patients.

Executive Summary

Breast cancer remains the second leading cause of cancer death among women. Although the incidence of breast cancer is lower among Black women, they are more likely to experience worse breast cancer care processes and outcomes compared to white women. New and developing genetic technologies and targeted therapies hold great potential to guide individualized high-quality cancer care; however, an unintended consequence could be increased disparities if such innovative technologies are not equally accessible across racial subgroups.

In 2004, a genomic innovation in breast cancer treatment, Oncotype DX® (ODX), became commercially available. For women with early-stage, estrogen receptor positive breast cancer, ODX predicts not only risk of breast cancer recurrence, but also the benefit of chemotherapy. ODX has already been incorporated into the clinical guidelines for node negative patients and is widely reimbursed by insurers, including Medicare and Medicaid. ODX results, which categorize women into low-, intermediate-, or high-risk groups, can improve treatment decision-making by avoiding the costs and risks associated with overuse of adjuvant chemotherapy among women who are unlikely to benefit from chemotherapy. Mixed evidence suggests that eligible Black patients may be less likely to utilize ODX testing compared to white patients. Reasons for these disparities and whether these disparities persist across diverse health care settings and insurers remain unclear. Furthermore, it is unclear whether subsequent chemotherapy initiation varies across racial subgroups in the presence

of ODX test results. This study contributes to the literature by exploring racial disparities in ODX uptake and subsequent adjuvant chemotherapy use across a large cohort of women treated in the community. Specifically, this dissertation has three objectives: 1) to characterize racial variation in the uptake of ODX among women with node negative and node positive breast cancer, 2) to characterize racial variation in adjuvant chemotherapy initiation among women receiving ODX testing, and 3) to understand the nuances in ODX and adjuvant chemotherapy decision making among oncologists caring for breast cancer patients.

To achieve these objectives, we used modified Poisson regression to examine the association between race and ODX testing and between race and adjuvant chemotherapy initiation among women in the Carolina Breast Cancer Study, Phase III cohort. We also conducted 15 semi-structured telephone interviews with oncologists to further understand provider and organizational level factors that influence the use of ODX testing and adjuvant chemotherapy initiation.

We found that ODX testing does not vary by race among node negative patients. However among node positive patients, Black women are less likely to receive ODX testing compared to White women. Currently, clinical and insurance guidelines recommend ODX testing only among eligible women with node negative, not node positive, breast cancer. Our qualitative work suggested that providers often order ODX testing for node positive within the context of an ongoing clinical trial. It is possible that racial differences among node positive women occur due lower clinical trial enrollment by minority patients, less favorable insurance policies, patient preferences or provider recommendation patterns. This racial difference in node positive patients reflects more guideline concordant care among African American women. Future research should examine more the role of these factors on racial variation in ODX test uptake for node positive patients. Specifically, it is unclear whether racial differences in the use of ODX testing by race are important and lead to differential quality of care and outcomes. Distinguishing between racial disparities verses racial differences in the uptake of newly emerging genetic technologies will be a challenge moving forward in the era of “precision medicine.”

Among women receiving ODX, race does not influence uptake of adjuvant chemotherapy across ODX risk groups. Instead, the ODX risk score, tumor characteristics and age influence

adjuvant chemotherapy uptake within risk groups. It is possible that the additional objective information provided by ODX reduces racial variation in chemotherapy uptake. Alternatively, the lack of racial differences may reflect broader recent research that has suggested narrowing racial disparities in adjuvant chemotherapy initiation.

Finally, oncologists identified organizational, interpersonal and intrapersonal factors that influence ODX use in clinical practice. Providers did not report variation in ODX testing by socioeconomic or racial characteristics. Instead, they discussed how clinical characteristics and patient preferences influence ODX test recommendations and chemotherapy initiation. Additionally, multi-level factors influenced the uptake of ODX testing in clinical practice. These factors appeared to vary across providers and their health care settings. Furthermore, providers reported that barriers to ODX testing that existed during early adoption have diminished over time. For example, we identified targets for facilitating the incorporation of this genetic technology into breast cancer care: Organizational structures, insurance coverage, and medical guidelines emerged as important organizational levers for facilitating the use of ODX testing, especially during early adoption. Future research should examine the association between organizational and provider level factors with ODX testing.

ODX testing offered an interesting model to study how rapidly expanding genetic tests can be used to guide precision medicine across racial subgroups. Overall, results from this study can inform key stakeholders about racial variation in the uptake of ODX testing and subsequent treatment decisions. Fortunately, ODX testing was equally accessed among node negative patients, for whom the test is covered and guideline concordant. Interestingly, African American women were less likely to receive ODX testing compared to non-African American women among node positive patients for whom the test is not yet widely covered nor included in clinical guidelines. This racial difference is interesting as it suggests potential racial differences in the early adoption of genetic technologies, yet also reflects more guideline concordant care among African American women. Taken together with qualitative results, insurance coverage and medical guidelines will be important policy levers for facilitating the use of genetic technology among all patients.

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CHAPTER 2. ONCOTYPE DX TESTING IN WOMEN WITH BREAST CANCER: STUDY RATIONALE

Background

Health Disparities in Cancer Care

National focus on health disparities came into the forefront following the 2003 Institute of Medicine's (IOM) report, *Unequal Treatment,* which brought attention to disparities in health care quality and outcomes among racial/ethnic minorities, low-income and other vulnerable populations.[1] From this report, IOM developed a working definition for health disparities "the difference in treatment or access not justified by the differences in health status or preferences of the groups."[1] This definition acknowledges a distinction between health differences and disparities, where a health difference fails to account for patient preferences and clinical appropriateness. Additionally as a result of *Unequal Treatment,* the National Health Disparities Report began providing an annual national view of health disparities in the US. The 2013 report demonstrated that health disparities persist across quality and access measures among all priority populations, including racial/ethnic minorities, low-income groups, women, children, the elderly, lesbian, gay, bisexual and transgender populations, disabled, and uninsured and rural populations.[1] Moreover, the majority of identified disparities in these groups have remained from year to year, demonstrating a need for innovative approaches for improving documented disparities.[2]

Racial disparities in cancer-specific mortality have persisted over the past 20 years.[3] In breast cancer, evidence suggests that racial disparities have not only persisted, but actually widened over time.[3] Biological factors may partially explain these disparities. Improvements in treatments that target certain types of breast cancer may partially contribute to widening disparities. While targeted therapies, such as trastazumab and endocrine therapy have been developed for human epidermal growth factor receptor 2 (HER2) positive and estrogen receptor/progesterone receptor (ER/PR) positive breast cancers, respectively, few new treatments have emerged for triple negative cancers, which are more common among Black women compared to white women.[3] Black women

are more likely to present with more aggressive tumor types [4]. However, even upon controlling for disease stage and treatment, disparities persist.[3] [5-9] For example, among hormone receptor positive breast cancers, Black women are more likely to experience poor health outcomes [10]. This is of particular interest, as hormone receptor positive breast cancer is associated with an improved prognosis compared to other breast cancer subtypes, yet disparities in health outcomes among Black women persist even upon controlling for tumor biology [10]. Thus, studies have demonstrated that even when controlling for biological differences, Black women still fare worse, suggesting that access and quality of care may contribute to existing disparities.

Racial disparities in breast cancer care processes and outcomes likely arise from a combination of biological, social and health system factors.[11] From screening to survivorship or mortality, racial/ethnic minorities fare worse on many quality and access measures.[2] The National Health Disparities Report demonstrated that racial/ethnic minorities, low-income populations, and those with public insurance (v. private) were less likely to have recommended mammogram screening;[2] even upon controlling for screening mammography and stage at diagnosis, racial disparities persist.[12, 13] This may be explained by concurrent differences in quality and access of care among breast cancer patients. Among women who develop breast cancer, multiple treatment quality and access disparities have been identified.[5, 10, 14-17] These treatment disparities may reflect differential access to, and quality of, cancer care among Black women. Black women were less likely to receive guideline concordant radiation therapy [2] and chemotherapy [5, 18] compared to white women. Furthermore, racial and socioeconomic disparities have been found among the use of targeted therapies such as trastazumab [19] for HER2 positive patients with metastatic breast cancer, and endocrine therapy for hormone receptor positive breast cancer patients [20]. This suggests that racial/ethnic minorities and low socioeconomic patients are less likely to reap the benefits of new targeted therapies compared to their white counterparts.

Genetic Technologies in Cancer Care

Increasingly, tumor genetics are being used to guide high quality cancer care. Cancer care is becoming increasingly personalized through the use of targeted therapies that are informed through the use of genetic technologies. These technologies have the potential to improve quality of care for

all women. Furthermore, if equally accessible to all racial/ethnic minorities, these technologies have the potential to account for biological differences in cancer etiology between racial/ethnic subgroups, potentially narrowing disparities in breast cancer processes and outcomes. However, if these technologies are not equally accessible across racial/ethnic subgroups, we risk widening existing disparities [21-23]. Thus, moving forward, health disparities researchers must also consider disparities in access to and use of genetic technologies in breast cancer care.

Evidence suggests that racial/ethnic minorities have lower access to innovative technologies compared to whites, including lower use of cancer predisposition genetic tests among Blacks compared to whites [22-24]. For example, Black women are less likely to access BRCA1/2 testing for breast and ovarian cancer prevention compared to white women [25]. These disparities in test receipt partially result from characteristics of the providers seen by racial/ethnic minorities: For example, Blacks are more likely to see providers or health care centers that are less likely to use these innovations [26, 27]. A qualitative study found that providers, patient advocates, executives and insurers identified similar barriers to the use of cancer predisposition genetic tests (e.g., BRCA1 test) and prognostic genetic tests (e.g., tumor gene expression panels for the management of breast cancer) [28]. Thus, it is also important to explore whether racial disparities exist in the uptake of tumor gene expression panels for the management of cancer.

Oncotype DX for the Management of Early Breast Cancer

Traditionally, decision tools have been crude for determining which early-stage breast cancer patients would most likely receive benefit from adjuvant chemotherapy, leading to its underuse or overuse relative to the associated costs and risks. A new genomic technology, Oncotype DX (ODX) was developed by Genomic Health (Redwood City, CA). Researchers examined the relationship between the expression of 250 candidate genes and the recurrence of breast cancer using tumor tissue from three clinical trials [29]. The candidate genes were selected because of their potential involvement in carcinogenesis, from evidence in the cancer literature, microarray data, genomic databases and molecular biology research. Gene expression was quantified using rt-PCR techniques from fixed, paraffin-embedded tumor tissue. Sixteen genes were found to be the strongest predictors of 10-year distant recurrence. Five control genes were chosen to normalize gene expression data:

these genes are not associated with carcinogenesis. Together, an algorithm was based around the expression of these 21 genes to compute a recurrence score that quantifies the likelihood of 10-year distance recurrence in patients with node negative, estrogen receptor positive breast cancer [29, 30]. This algorithm was validated to predict 10 year distant recurrence using data from the National Surgical Adjuvant Breast and Bowel Project Trial B-14 [30].

ODX leverages tumor gene expression patterns using the validated algorithm to predict risk of 10 year distant recurrence: The algorithm groups genes into functional groups (i.e., reference (or control genes), proliferation, invasion, HER2, GSTM1, CD68, BAG1 and Estrogen) and calculates a "risk of recurrence score" which correlates to a percent risk of distant recurrence at ten years. These risk scores are divided into three risk groups: low (score<18), intermediate (score 18-30) and high (score >30). The test not only predicts a woman's risk of breast cancer recurrence, but also the benefit to chemotherapy; thus, it may be a useful tool for providers and patients during adjuvant chemotherapy decision-making [29, 30]. Women with low risk tumors are unlikely to receive any clinical benefit for using adjuvant chemotherapy, whereas women with high risk scores receive a significant improvement in ten-year distant recurrence outcomes.[29] The benefit for adjuvant chemotherapy in the intermediate risk group is less clear: for these women, clinical-pathological and preference based decision-making may be appropriate. The Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) is currently in progress to acquire more information about women in the intermediate risk group. The TAILORx trial is randomizing women with intermediate ODX risk scores (defined as ODX risk score=11-25 for the trial) to anti-estrogen therapy (i.e., tamoxifen, aromatase inhibitors) only or antiestrogen therapy plus adjuvant chemotherapy.[31]

Currently, evidence is building for ODX testing not only for node negative patients, but also for women with early stage, lymph node positive disease [32-34]: An ongoing trial RxPONDER will provide more definitive evidence around whether ODX should be used among women with one to three positive lymph nodes [35]. It is important to note, that development and validation of ODX occurred from the tumors of women taking Tamoxifen [29, 30, 36]. Because these women were on Tamoxifen, it is unclear whether the Oncotype DX algorithm predicts the natural history, 10-year distant recurrence, or if the algorithm predicts a woman's responsiveness to endocrine therapy.

Since the original study validating ODX, evidence has mounted to support the prognostic [37] and predictive value of the test [38]. Exempt from FDA approval, ODX became commercially available in 2004. Insurance reimbursement for the test began in 2005 by a commercial insurer [39], and by 2006 CMS began reimbursing the test [40]. ODX was subsequently added to the guidelines in 2007 and 2008 by ASCO and NCCN, respectively.[39] Today, many large insurers cover the test [39], as evidence suggests prognostic and predictive validity for the test and potential cost savings [39, 41-45]. On a population level, evidence suggests that ODX influences chemotherapy treatment decision-making [46-54], reducing the overuse of chemotherapy [52-55]. ODX may increase providers' confidence in the chemotherapy decision-making process [47], and patients have reported that they would recommend ODX to other breast cancer patients [56].

Uptake of Oncotype DX (Aim 1)

About half of all women with invasive breast cancer may be eligible for and benefit from ODX [57]. However, uptake of ODX varies across study settings, ranging from 10%-50% of *eligible* women receiving the test. This suggests potentially suboptimal use of the test among eligible patients.[58, 59] [60] Unfortunately, early descriptive evidence suggests that Black women are less likely to receive this test compared to white women [58, 60, 61], even when controlling for disease characteristics.[61] To my knowledge, only five studies describe the uptake of ODX by race.[27, 58, 59, 61, 62] Of these five studies, three reported racial disparities in its use, with the proportion of Black women who received ODX being an average of 10% lower compared to white women.[58, 60, 61] Two studies found no racial differences in ODX testing; however, the generalizability may be limited as one was conducted within a single academic, comprehensive cancer center [59] and the other was conducted among women ages 65 or older with Medicare [62]. Only two studies directly examined racial disparities in ODX testing as part of their primary analyses. [58, 60] Unfortunately, the generalizability of these studies is also limited as they examine patient-level factors within a homogeneous patient population: one within a single urban population [60] and the other within three academic medical centers [58]. Furthermore, while several articles have investigated racial variation in the uptake of ODX testing, little is known about <u>why</u> these racial disparities in test uptake exist. One study suggests that Black women may more likely be seen in hospitals with low uptake of ODX,[60] suggesting that

system-level factors influence the ODX testing among patients. However, it is likely that additional patient level factors influence the ODX testing. Reasons for racial disparities in ODX testing may consist of biological (e.g., more aggressive tumor biology) and social factors (e.g., access to care) on the patient level. Studies investigating patient level factors that influence ODX test receipt and disparities will fill a gap in the literature regarding who has access to genomic technologies in cancer care.

Chemotherapy Decision-Making with Oncotype DX (Aim 2)

In addition to potential disparities in the uptake of ODX, it is unclear whether racial variation exists in adjuvant chemotherapy decision-making when ODX test results are available to the provider. A number of studies indicate that minority women are less likely to receive guideline-concordant, primary course of treatment for breast cancer.[63] Similar results have been found for adjuvant care. Black women across health care insurers appear to be less likely to receive guideline-concordant adjuvant chemotherapy compared to their white counterparts.[5, 8, 18, 64] Differences in adjuvant chemotherapy use may emerge during the treatment decision-making process. Thus, it is of interest to understand whether a technology, such as ODX testing, influences adjuvant chemotherapy decision-making differentially among racial subgroups. Only one study has examined racial differences in chemotherapy use among women who receive ODX score results.[58] Interestingly, the study found no racial differences in chemotherapy use within ODX risk groups. However these results may not be generalizable, as the study was conducted within three academic-affiliated Atlanta hospitals. Furthermore, this study's evaluation of treatment outcomes was limited by small sample size. Studies conducted in diverse settings are necessary to characterize how ODX scores impact adjuvant chemotherapy initiation across racial subgroups in order to inform policy and interventions which aim to improve adjuvant chemotherapy decision-making.

Multilevel Factors Associated with Oncotype DX Use (Aim 3)

Prior genomic research indicates that the diffusion of genomic innovations is influenced by organizational (i.e., health care system), interpersonal (i.e., provider) and intrapersonal (i.e., patient) level factors [65]. Thus, it is important to consider not only patient characteristics' influence on ODX test receipt and adjuvant chemotherapy initiation, but also provider and organizational characteristics.

The lack of a multilevel framework to model ODX testing is partially due to data-constraints, as secondary datasets rarely include provider and organizational level factors that influence the receipt of ODX testing across diverse health settings (i.e., public/private, academic/non-academic, and urban/rural health care centers) [58, 60, 61, 66]. To date, two studies have examined whether site of care influences ODX receipt.[27, 61] The authors found that women treated at municipal hospitals were less likely to receive ODX testing compared to those being seen at tertiary hospitals.[27] Interestingly, Black women were more likely to be seen at municipal facilities, suggesting that site of care is a partial source of the racial disparity in receiving ODX testing. Another study found that women who were seen at a comprehensive cancer center were more likely to receive gene expression profiling tests compared to those seen in the community.[61] These studies provide supporting evidence for taking multilevel approaches in examining disparities in the use of ODX testing.

Two qualitative studies have used provider interviews to examine provider and system-level factors that influence the ODX testing in clinical care.[28, 67] Study findings indicated that characteristics of the test (i.e., interpreting intermediate results)[67], test coordination (including reimbursement) [28], patient out-of-pocket costs [28], and the use of multidisciplinary teams [67] created barriers to the use of this technology in clinical practice. Furthermore, oncologists worried that testing could be used inappropriately [67] or result in treatment delays [28]. One study focused on barriers to the *ordering* ODX testing, while the other study focused on *how* the test is used in clinical practice [28]. However, neither explored both issues of uptake and use of the test results, nor were conceptual frameworks used to explicitly examine provider and organizational factors. Ordering ODX testing and subsequent adjuvant chemotherapy is a nuanced decision process, and quantitative analyses alone may not capture how ODX is used in decision-making. Thus a need remains to conduct a theory driven, qualitative study that explores both *why* the test is ordered/not ordered and *how* the test result is used in clinical decision-making.

Rationale

Significance

Advances in genetics have improved our understanding of the molecular basis for cancer.

Today, we recognize that breast cancer is not one single disease, but rather a complex set of diseases that can be characterized by genetic markers. The genetic characteristics of a tumor can predict risk of recurrence and can be used to tailor therapeutics to the individual, providing high-quality, patient-centered cancer care [68]. However, if genomic innovations are not accessed equally and used appropriately across racial groups, an unintended consequence of this technology may be to exacerbate current racial disparities in the process and outcomes of cancer care [58].

ODX, an example of such a genomic technology, has demonstrated prognostic and predictive validity [69-71]. Thus, ODX was added to the American Society of Clinical Oncology guidelines in 2007 and National Comprehensive Cancer Network Breast Cancer Treatment guidelines in 2008; in addition, Medicare began reimbursing for ODX in 2006. By personalizing cancer treatment plans, ODX testing has the potential to improve overall processes and outcomes of care for women with breast cancer. However, research demonstrates that Black women are less likely to receive ODX testing compared to white women with similar disease characteristics [58, 60, 61], which may exacerbate racial disparities in cancer care. Current literature regarding race and ODX testing is largely descriptive and has not identified factors that are associated with racial disparities across different health care systems, nor has the literature demonstrated that this innovation impacts adjuvant chemotherapy initiation equivalently across racial subgroups.

This project seeks to address this gap in knowledge by identifying whether racial disparities exist in the uptake of ODX testing, as well as adjuvant chemotherapy initiation based upon ODX results. This contribution will be significant as it can inform evidence-based interventions and policies that increase access to genomic technologies (such as ODX) and improve quality of, and access to, cancer care for minority patients. The goal of this study is aligned with the mission of the NCI “to assess the incorporation of state-of-the-art cancer treatments into clinical practice.[72]” Although this study focuses solely on ODX testing, genomic technologies will continue to become available to personalize treatment and to improve the outcomes of cancer patients, particularly as the federal government moves forward with “precision medicine” efforts. Understanding if and why these uptake disparities exist and how test results are used to inform treatment decisions can help to identify strategies that attenuate chasms in the process and outcomes of cancer care.

Innovation

The proposed research is innovative in four important ways. First, it is the first study to examine uptake of ODX testing by racial subgroup across diverse health settings (i.e., public/private, academic/non-academic, and urban/rural health care centers) and insurers [58, 60, 61, 66]. Although two published studies examined racial disparities in the uptake of ODX testing [58, 60], their generalizability is limited as they examine patient-level factors within a single urban population [60] and within academic medical centers [58]. This is problematic, because prior genomic research indicates that the diffusion of genomic innovations is influenced by organizational, provider and patient level factors [65]. The lack of diverse patient populations and care settings is partially due to secondary datasets rarely including data about ODX testing and results across diverse health care settings and insurers. Second, it is the first study to determine whether ODX risk score is associated with similar probabilities of adjuvant chemotherapy initiation by racial subgroup across a diverse patient population. Only one other study has examined racial disparities and adjuvant chemotherapy use among women receiving ODX testing. The study was underpowered and only examined health care use among patients seen within three academic medical centers, limiting the generalizability of study findings.[58] Third, the proposed study analyzes data from a rich and unique dataset that includes diverse health care settings and insurance plans throughout North Carolina to examine racial disparities in genomic testing in cancer care. To date, secondary data analyses have utilized claims-based datasets, which often restrict the sample to a single payer population or medical records from a single medical center. Instead, we levered the phase III, Carolina Breast Cancer Study (CBCS-III) data to examine racial disparities. This data set includes both survey and medical record abstraction data for women across NC. Both ODX testing and results have been abstracted from the medical record, allowing for the analysis of racial disparities in the uptake of ODX and its use in treatment in a diverse patient population. Also, CBCS-III oversamples Black breast cancer patients, making this dataset ideal to examine racial disparities in breast cancer care. Finally, the approach uses mixed-methods to capture multilevel factors that influence ODX uptake and use in clinical practice. In-depth interviews with oncologists who deliver care across diverse health care settings provide important insights about strategies to increase ODX uptake when caring for women with breast cancer. Taken

together, this study elucidates factors that future clinical and policy interventions can target to increase the use of genomic technologies, such as ODX testing, among minority populations.

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CHAPTER 3: METHODS

I have organized the Methods section by Specific Aims. First, I have described the Methods for Aims 1 and 2, including the General Approach, Conceptual Model, Hypotheses, Data Sources, and Analytical Plans. Second, I have described Aim 3, using the same structure. The rationale for organizing the Methods in this way is that Aims 1 and 2 are quantitative analyses of CBCS-III, while Aim 3 uses qualitative methods: Such a structure should reduce redundancy.

Aims 1 and 2 Methodology

General Approach

Aim 1: Characterizing which patients received ODX testing provides information regarding who has access to genomic technologies in clinical practices across health care settings. In particular, I sought to examine whether ODX test uptake varies by race; if so, this may contribute to our understanding of racial disparities in breast cancer care and outcomes. The *objective of aim 1* was to determine whether differences in ODX test receipt in clinical practice have occurred by race. To attain this objective, I tested the working hypothesis that white women were more likely to receive ODX testing compared to Black women. To this end, my approach was to model the uptake of ODX testing using a multivariate regression model and controlling for patient level factors. The *rationale* for this aim was to fill a gap in current knowledge about the uptake of ODX across racial groups and across diverse health care settings. In the age of precision medicine and targeted therapies, we must elucidate the relationship between the uptake of genomic innovations and race in order to better understand how these new technologies may influence racial disparities in cancer processes and outcomes. From this study, I expected to understand whether racial disparities emerge in the receipt of ODX testing among early-stage breast cancer patients in North Carolina. The results from this aim can inform clinicians, policy makers and researchers about whether there is a need to implement interventions to increase patients' access to genomic technologies, particularly among certain racial subgroups.

Aim 2: Determining the effects of race and ODX risk group on adjuvant chemotherapy initiation will elucidate whether there are racial differences in how the test results are used in treatment initiation. The objective of this aim sought to identify whether racial differences occur in adjuvant chemotherapy initiation among women with similar ODX risk scores. For this objective, I tested two working hypotheses: (1) Black women in the low and high risk groups would be less likely to initiate guideline-concordant adjuvant chemotherapy compared to white women and (2) Black women in the intermediate risk group would be less likely to initiate adjuvant chemotherapy compared to white women. I tested these hypotheses using the approach of multivariate modeling techniques to elucidate chemotherapy initiation within the CBCS-III dataset. The rationale for this aim was to identify whether racial differences existed in treatment decisions in the presence of ODX risk information. This information is critical in understanding the impact of ODX test results on racial differences in breast cancer processes, and may inform interventions that improve the use of test results across racial groups. When completed, my expectation was to have identified whether there are racial differences in chemotherapy initiation, accounting for ODX risk score. This evidence would allow policy makers to create interventions that impact how genomic technologies are used among breast cancer patients, particularly minority patients.

Conceptual Model: Andersen's Behavioral Model

Andersen's behavioral model of health care utilization guided the analysis for Aims 1 and 2 (Figure 1) [1]. Andersen's behavioral model of health services use demonstrates how environmental factors and population characteristics influence health care utilization.[1] In particular, the model suggests population characteristics, including predisposing characteristics, enabling resources, and needs, influence ODX test receipt. A woman's need for ODX testing is determined by predisposing factors and mediated by enabling resources.

Predisposing Characteristics. A large body of evidence has demonstrated that race influences breast cancer processes and outcomes.[2] More specifically, studies demonstrate that Black women are less likely to receive ODX testing compared to white women. [3-5] Predisposing factors also include socio-cultural factors that are associated with race and health care utilization, for example, attitudes and beliefs, mistrust of the medical system, and structural racism. [2, 6-8]

Enabling Resources. The ODX test is a complex and expensive tumor gene expression test. Thus, education, income, employment, insurance status and social support [2, 9-11] may act as enabling resources for the use of ODX, where more educated women and women with more financial and social resources might be more likely to access ODX. According to the IOM's definition of health disparities, both measures of SES and race/ethnicity together measure health disparities in the US.

Need. Clinical characteristics such as tumor size, stage, grade, receptor subtype, nodal involvement and treatment type influence the perceived need for ODX testing. These characteristics influence a patient's need for chemotherapy decision-making support through the use of ODX testing.[9] Black women are more likely to have more aggressive tumor characteristics and this may impact whether a patient receives ODX testing. For example, if a provider observes high-risk tumor characteristics, then he/she may bypass ODX testing and automatically recommend adjuvant chemotherapy. Other clinical predisposing factors such as age [12] and comorbidities [10] may also influence chemotherapy decision-making, where women who are very frail or who suffer from extensive co-morbidities may be less likely to receive ODX testing, as chemotherapy may be contraindicated, negating a need for the test. On the other hand, it is possible that women who are frail or who suffer from co-morbidities may be in higher need of ODX testing to provide reassurance that chemotherapy is not necessary. Either way, it is likely that these clinical characteristics influence ODX testing in one direction or another.

Other factors. Andersen's model also describes how external factors influence health care use. We did not control for factors arising from the environment and outcomes. However, we did control for year of breast cancer diagnosis, as the year may influence whether ODX was being widely used by providers. By 2008, when recruitment into CBCS-III began, ODX had been added to clinical guidelines and was being covered widely by CMS and private insurers [13]. Roger's theory of diffusion, suggests that the use of an innovation changes over time, where diffusion of the innovation across time can be depicted by an "S-shaped" curve. Along this curve, individuals represent the (1) early adopters, (2) early majority, (3) late majority, (4) laggards and non-adopters of the technology [14]. Thus, it was important to control for year of diagnosis, as the uptake of ODX has increased over time [15].

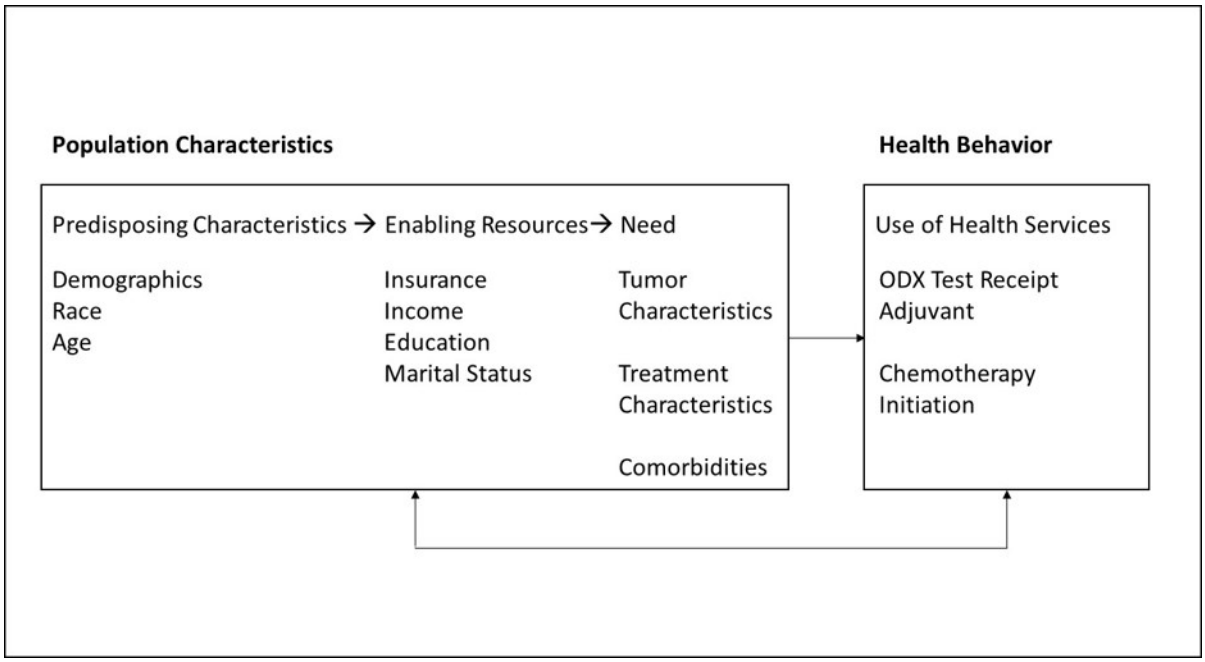

Figure 1. Andersen's behavioral model (adapted) for health care utilization informed empirical models for Aims 1 and 2.[1]

Just as the model frames how race, a predisposing characteristic, influences whether a patient receives ODX testing, the model frames how race may influence adjuvant chemotherapy initiation (Aim 2). Researchers have documented lower rates of guideline-concordant chemotherapy among Black women [8, 10, 12, 16], suggesting that Black women may be more likely to forgo chemotherapy. The aforementioned predisposing, enabling and need variables, influence not only ODX test receipt, but also chemotherapy initiation. Predisposing characteristics, including socioeconomic factors (such as education, income, employment status, insurance) [9]and social support, may influence chemotherapy use.

In Aim 2, ODX test results were added to the analytic model. The ODX test result, a need variable, reflects a patient's need for adjuvant chemotherapy. Thus, race interacted with ODX risk scores would demonstrate whether racial differences in chemotherapy initiation occur by risk score (where risk scores are categorized into three groups: low-, intermediate, and high- risk groups).

Hypotheses

Question 1: To what extent is race associated with the uptake of ODX? Hypothesis 1: ODX test receipt are lower among Black patients compared to white patients, controlling for clinical

characteristics.

Question 2a: To what extent is race associated with the initiation of guideline-concordant adjuvant chemotherapy? Hypothesis 2a: Black women are less likely to receive guideline-concordant chemotherapy within the low and high-risk groups compared to white women.

Question 2b: Is race associated with the initiation of guideline concordant adjuvant chemotherapy among women with intermediate risk scores? Hypothesis 2b: Black women are less likely to initiate adjuvant chemotherapy within the intermediate risk group compared to white women.

Data Source

Data included baseline, pathology report, and medical record abstraction data from phase III of the Carolina Breast Cancer Study (CBCS-III) (NIH 8389741). This dataset contains data on 2.998 women, age 20-74 years with invasive breast cancer who were enrolled in the study between 2008 and 2013. Participants were identified through rapid case ascertainment in collaboration with the North Carolina Cancer Registry**[17]**. Women were included in the study if they had an incident primary invasive breast cancer diagnosed, and if they were North Carolina residents at the time of diagnosis. These women were enrolled across the state of North Carolina, representing 44 counties, including both rural and urban counties.

Patients were randomly sampled from four strata: Black women under 50 years old, Black women 50 years or older, non-Black women under 50 years old, and non-Black women 50 years or older, where the sampling fraction (f=n/N, n=sample size and N equals the population size) was 100%, 60%, 40% and 15%, respectively [18]. Thus half of this cohort was composed of Black women, and the remaining half was non-Black. This makes these data particularly amenable to racial health disparities research. CBCS-III data are unique as they include both survey and medical record abstraction data for women who are being treated across diverse health care settings (i.e., public/private, academic/non-academic, urban/rural) and insurance types (i.e., public, private, uninsured). In the study, a nurse interviewed participants at baseline, and the patients completed a quality of life questionnaire and provided consent for medical record abstraction, providing both self-reported and abstracted medical record data [17, 18]. Two abstraction forms capture medical record data: the medical record abstraction form and the medical record abstraction pathology report form

(Table 1). Thus, these rich data provided a comprehensive look at how ODX testing has been used, across a diverse population in North Carolina.

Eligibility Criteria

Eligibility criteria for women in the CBCS-III dataset were: (1) estrogen receptor positive (ER+) breast cancer, as ODX testing has been approved for use within this patient population[19], and (2) early, non-metastatic disease (i.e., AJCC stage III-IV patients were excluded), because chemotherapy decision-making process is quite different in this patient population and ODX testing has not been validated within this patient population, (3) HER2 negative, because ODX testing is not approved for these patients, (4) patients with undetermined tumor grade, and (5) patients with missing data.[20] We estimated that 1439 women (602 Black women, 837 white women) would meet these eligibility criteria. Given this sample size, our preliminary sample size calculation suggested that we would be able to detect effect sizes of 10-15% with 80% power; this effect size reflected a minimal clinically significant difference. Our total sample size was 1468 women; thus, we had enough power to detect 10% differences in ODX test receipt by race. This supports the AHRQ definition of health disparities, which detects racial disparities as differences of 10% or greater [21].

Aim 2 analyses were further limited to those women who received ODX testing and had an ODX test result abstracted from their pathology records. We estimated that 651 women (417 Black women, 234 white women) would meet these criteria. A preliminary sample size calculation suggested that we would be able to detect crude effect sizes of 15-25% with 80% power. Our total samples size was 544 women; we have enough power to detect effect sizes of ~15% in the intermediate group, and ~20% in the low risk group, and ~35% in the high risk group.

Descriptive Analyses

Aim 1. Descriptive statistics were calculated using population weights to account for the stratified sampling strategy used to collect CBCS-III data. We also accounted for clustering at the provider. We described clinical and demographic differences between (1) women who received ODX testing compared to those who did not, and (2) Black women and white women in the sample using weighted linear regression for continuous variables and weighted chi2 test for binary/categorical variables.

Aim 2. Descriptive statistics were calculated using population weights to account for the stratified sampling design. We also accounted for clustering at the provider. Weighted linear regression for continuous variables and weighted chi2 test for binary/categorical variables compared the characteristics (especially race) of women who initiated adjuvant chemotherapy compared to those who did not initiate adjuvant chemotherapy, by ODX risk group. Also, we plotted the distribution of raw ODX risk scores by race within each risk group in order to describe the distribution of raw risk scores within each risk group by race. Finally, we plotted the distribution of raw ODX risk scores by nodal status.

Primary Analyses

Aim 1. For the primary analysis, we used a modified Poisson regression with robust standard errors. We explored logistic regression modeling to determine whether race influences the likelihood that an individual receives ODX. Logistic regression models address out of range predictions and heteroskedasticity that can result from using ordinary least squares approaches (linear probability modeling) when the outcome variable is binary. However, model convergence can be difficult with logistic regression models, furthermore, logistic regression models produce odds ratios, which can be difficult for readers to interpret. As such, we considered several other models. First we considered reverting back to the linear probability model: However, this model yielded predictions that were out of range (that is predicted probabilities that were greater than 1 or less than 0) over 8% of the time. Second, we considered the Poisson and Binomial models. Like logistic regression, the Binomial models (generalized linear model with the Binomial family and log link) can experience problems with model convergence: This was the case in our study. Poisson regression with a sandwich error term estimates relative risk consistently and efficiently with correlated binary outcomes.[22, 23] Furthermore, this approach easily produces a risk ratio, which is a more intuitive result to report to lay audiences. Thus, this approach was used to estimate the effect of race on ODX test receipt. It is important to note that all models yielded similar regression results.

Complex survey design was addressed through sample weights and design effects using Taylor Series Approximations in STATA (StataCorps, College Station, TX): both sampling weights

and strata were implemented. Using sample weights provided parameter estimates that represent the population, not just the sample.

Theory suggested that it may be necessary to stratify analyses for node status, as the reasons for ordering ODX testing may vary by node status. In order to do this, I tested the null hypothesis that $H_0 = \Pr(y=1|x, Z)_{\text{node positive}} = \Pr(y=1|x, Z)_{\text{node negative}}$. We failed to reject the null hypothesis: Risk ratios for the association between race and ODX testing differed by nodal status. Furthermore, qualitative data suggested that providers used different criteria when deciding to use ODX for node positive compared to node negative patients. Thus, models were stratified by nodal status for Aim 1.

IOM's definition of health disparities is "the difference in treatment or access not justified by the differences in health status or preferences of the groups".[24, 25] This definition acknowledges race as a social construct [24, 25]. Thus, SES variables were not included in our primary models for identifying racial disparities: These models were referred to as the "primary models." "Secondary models" were run, which included SES variables.

The empirical models are below:

Primary Model: $ODX\ test\ receipt = \beta_0 + \beta_1 Race + \beta_2 tumor\ characteristics + \beta_3 treatment\ characteristics + \beta_4 comorbidities + u$

Secondary Model: $ODX\ test\ receipt = \beta_0 + \beta_1 Race + \beta_2 tumor\ characteristics + \beta_3 treatment\ characteristics + \beta_4 comorbidities + \beta_5 socioeconomic\ factors + u$

$$\text{Prob}\left(y_i \mid \lambda\right) = \frac{e^{-\lambda}\lambda^{y}}{y!}$$

for y=0,1

The key dependent variable in Aim 1 is receipt of ODX testing (Table 1), which was abstracted from the medical pathology reports. This begs the assumption that if ODX testing was ordered, it was noted in the pathology reports. The key independent variable in this aim was a binary indicator for

race (i.e., Black and non-Black (i.e., White, Asian, other), which was obtained from the baseline survey. Covariates included the following: tumor characteristics (such as tumor stage, size, grade, progesterone receptor status), treatment characteristics (i.e., surgery type and radiation), comorbidities (i.e., diabetes, obesity, COPD, hypertension and heart disease), and year of diagnosis. Socioeconomic variables (i.e., income, insurance status, education, age) were included in our secondary model.

Prior to inclusion in the model, we used pair-wise correlations to determine whether significant multicollinearity occurred between certain variables (e.g., tumor stage and tumor size). Decisions on which variable to exclude were made based on which variables were the most clinically and theoretically appropriate for the construct of interest. Tumor stage, size and grade were highly correlated. Thus, tumor stage was removed from the model, as it incorporates size and grade and therefore does not account for new information to the model. Instead tumor stage was only used to determine inclusion criteria (Stage I and II were included in Aims 1 and 2). Radiation receipt and surgery type (i.e., binary variable: lumpectomy vs. mastectomy) were highly correlated, as the vast majority of women receiving a lumpectomy also received radiation per NCCN guidelines. For this reason, radiation was not included in the final analysis, however we did look at radiation initiation descriptively (Table 1). Finally, we used sensitivity analyses to evaluate whether the race-ODX test association varied in smaller (<0.5 cm) verses larger (>=0.5 cm) tumors, and found no substantial differences between strata. While some guidelines do not recommend ODX testing on<0.5cm tumors, we included women with <0.5cm tumors in our analysis, as we wanted to retain as much of our sample as possible.

Aim 2. For the primary analysis, we used the modified Poisson regression with robust standard errors to determine whether race influenced the likelihood that an individual initiated adjuvant chemotherapy, controlling for the ODX test result (see empirical models below). We stratified our analyses by ODX risk groups, as reasons for taking adjuvant chemotherapy would likely vary by risk group given differential treatment guidelines for each stratum. This decision was supported by sensitivity analyses, which indicated that a pooled analysis would be inappropriate.

Thus, three models assessed adjuvant chemotherapy initiation across the three risk strata. Models A and B assessed the impact of race on the initiation of adjuvant chemotherapy in the low and high risk groups, respectively, where there are clear guidelines regarding adjuvant chemotherapy decision-making (i.e., women with low risk scores are recommended to forgo chemotherapy, women with high risk scores are recommended to initiate chemotherapy). Model C assessed the association between race and the initiation of adjuvant chemotherapy among women with intermediate ODX risk scores, for whom chemotherapy guidelines are less clear. For the reasons described above (Aim 1), modified Poisson regression was used, accounting for complex survey design with sample weights and design effects using Taylor Series Approximations in STATA. Risk ratios were reported.

Sensitivity analyses suggested that node negative and node positive patients could be pooled for analysis. Analyses within the high-risk group were exploratory due to small sample size (n=53), and only a crude model was reported. Below are the empirical models:

Models A and B, Primary Model: $Chemotherapy\ Initiation = \beta_0 + \beta_1 \mathbf{Race} + \beta_2 ODX\ risk\ group + \beta_3 treatment\ characteristics + \beta_4 comorbidities + u$

Models A and B, Secondary Model: $Chemotherapy\ Initiation = \beta_0 + \beta_1 \mathbf{Race} + \beta_2 ODX\ risk\ group + \beta_3 treatment\ characteristics + \beta_4 comorbidities + \beta_5 socioeconomic\ factors + u$ for y=0,1

Model C, Primary Model: $Chemotherapy\ Initiation = \beta_0 + \beta_1 \mathbf{Race} + \beta_2 ODX\ risk\ score + \beta_3 treatment\ characteristics + \beta_4 comorbidities + u$

Model C, Secondary Model: $Chemotherapy\ Initiation = \beta_0 + \beta_1 \mathbf{Race} + \beta_2 ODX\ risk\ score + \beta_3 treatment\ characteristics + \beta_4 comorbidities + \beta_5 socioeconomic\ factors + u$ for y=0,1

The key dependent variable in Aim 2 was adjuvant chemotherapy initiation (Table 1), which was abstracted from each patient's medical record. The key independent variable was a binary indicator for race (i.e., Black and non-Black).

Covariates included those used in Aim 1, as these factors influence not only whether a patient receives ODX, but also whether they receive adjuvant chemotherapy. These covariates included the following: tumor characteristics (such as tumor size, grade, progesterone receptor

status), treatment characteristics (i.e., surgery type), comorbidities (i.e., diabetes, obesity, COPD, hypertension and heart disease), and year of diagnosis. Socioeconomic factors (i.e., income, insurance status, education, age, ethnicity) were not included in the Primary Models, but were included in the Secondary Models. As previously mentioned, covariates were tested for multicollinearity using pair-wise correlations: tumor stage and radiation initiation were excluded from the models as described in Aim 1. Due to sample size constraints, we did not further stratify analyses by nodal status; however, nodal status was included as a covariate in these models. Also, ODX risk score was added as a covariate within each stratified analysis.

Secondary Analyses

Aim 1. We employed propensity weighted models to determine the average treatment effect of race on receiving ODX testing. Propensity score weighting may address small sample size and large number of covariates. This approach prevents the loss of degrees of freedom by allowing the inclusion of all of the covariates in one measure. Because the mode of implementation of propensity scores can yield different results, we conducted sensitivity analyses comparing propensity score weighting with matching (using the Greedy matching technique [26], using STATA code gmatch). Results from propensity score weighting and matching can differ due to limited availability of matches and sensitivity of weighted estimates to outliers.[27] In our analyses, results were consistent across propensity score weighting and matching (Appendix 1). To allow us to use all observations in the sample, we implemented propensity score weighting for our analysis.

Aim 2. As a secondary analysis, we employed propensity weighted models to determine the average treatment effect of race on ODX use. As a sensitivity analysis, we also conducted propensity matched models, using the Greedy Matching method, and found similar results to those found using propensity weighted models (Appendix 1).

As an exploratory aim, we compared endocrine therapy initiation across racial subgroups and by ODX risk group using weighted chi-square tests.

Expected Outcomes. The expected outcomes of this study were to understand (1) whether the likelihood of ODX test receipt varies by race, and (2) how ODX results are used in making

treatment decisions for Black versus non-Black women with breast cancer across different risks. This outcome *attains this study's objective* of determining whether differences in ODX testing in clinical practice have occurred by race, and whether there are racial differences in adjuvant chemotherapy initiation among those with ODX test results. This helps *attain this proposal's overall goal,* as the *expected outcomes* elucidate whether race influences ODX test receipt and can be targeted in future interventions that aim to increase access to ODX testing and subsequent guideline concordant adjuvant chemotherapy use.

Table 1. Variables of Interest

Variables in Models & Descriptive Stats

	Aim	Variable	CBCS3 Code name	Original Coding/Categories	Data Source	Variable/Sample Specification
Clinical Characteristics	1-2	Year of Diagnosis of BC	DX DATE	Date (MM/DD/YYYY)	Med Rec Abs	Year: Dummy Variable (2008-2013) (2012 and 2013 were collapsed due to small cell size)
	1-2	Age at Diagnosis	AGESEL	20-74	Survey	Binary: above and below 50 years of age
	1-2	Comorbidities	COMORB_COMP_1-10	See attached Excel	Med Rec Abs	Count: Includes the number of ICD-9 codes from the following categories: Obesity, Diabetes, Hypertension, COPD, Heart Disease
	2	Nodal Status	NODESTAT	1=Positive, 0=Negative	MA_VARS	Binary: N0=negative, remainder positive (node positive were N1)

Treatment Characteristics	1-2	Tumor Size	ESTSIZE	1 = < 2 cm, 2 = >2-5 cm, 3 = >5 cm	MA_VARS	Dummy Categorical < 2 cm, >2-5 cm, >5 cm
	1-2	Tumor Grade	GRADE	1 = Well differentiated, 2 = Moderately differentiated, 3 = Poorly differentiated, 4 = Undifferentiated, 9 = Not determined	Med Rec Abs	Dummy Categorical: Grade==9 excluded; Combined Nottingham Histologic grade
	2	Oncotype DX Score	ONCO_DX _SCORE	Count	Path	Count: 1-100 & Group (Low score 18 or less, Intermediate >18-31, high score >31)
	1-2	PR Status	PR_STS	Negative, Weak Positive/Borderline, Positive	Path	Binary: Pos=weak/borderline & positive Neg= Negative
	1-2	Surgery	SURG	See CBCS3 Code Book for full list of surgery types	Med Rec Abs	Binary : Lumpectomy/Mastectomy: mastectomy = yes, if she has any first course SURG==30-80), lumpectomy==yes (if she has any first course SURG==20-24 and has no SURG==30-80
Key Independent Variable	1-2	Race used in Sampling	RACE	1=non-Black/0=Black	Survey	Binary

Dependent Variables	1	ODX Included?	ONCO_DX_ASSAY_INCLUDED	Yes/No	Path	Binary: Yes/No
	2	Adjuvant Chemotherapy Initiation	ADJCHEMO2	Yes/No	Med Rec Abs	Binary: Yes/No First course adj chemo (after surgery)
Variables for Descriptive Statistics						
		Variable	CBCS3 Code name	Original Coding/Categories	Data Source	Variable/Sample Specification
Descriptive Treatment Variables	1-2	Radiation Initiation	RAD_START_DATE	Date	Med Rec Abs	Binary: Yes/No
	1-2	Adjuvant Chemotherapy Initiation	CHEMO_START_DATE & Diagnosis Date	MM/DD/YYYY	Med Rec Abs	Binary: Yes/No, Adjuvant chemo, chemo after first course surgery
	1-2	Hormonal Therapy Initiation	HORM_START_DATE	MM/DD/YYYY	Med Rec Abs	Binary: Yes/No First course therapy
Descriptive/SES Variables	1-2	Income 2	MONEY	1 = 15-30K 2 = 30-50K 3 = >50K 4 = <15K 5= Not Reported	Survey	Dummy Categorical
	1-2	Insurance type	P2I2, P3I3A, P3I3B, P3I3C, P3I3D, P3I3E, P3I3F	Question I2: Do you currently have health insurance coverage? Question I3: What type of health insurance do you have now? (check all that apply).	Survey	Binary: Medicare, Private, Medicaid, Uninsured
	1-2	Education 2	EDUCAT	1 = HS & Post HS 2 = College+ 3 = < HS	Survey	Dummy Categorical
	1-2	Employment	P3H7A, P3H7B	Yes/No/Not reported	Survey	Binary: Yes/No

	1-2	Marital Status	P3H1	1 ___ Never married or lived as married, 2 ___ Married, or living as married, 3 ___ Widowed, 4 ___ Separated, divorced, or no longer living as married, 9 ___ NA	Survey	Binary: Married=Married or living as married, Not Married = never/lived as married, widowed, separated, divorced or no longer living as married, NA From the baseline survey, item H1.
Variables for Sample Selection and Stratification						
		Variable	CBCS3 Code name	Original Coding/Categories	Data Source	Variable/Sample Specification
Sample Specification: Clinical/Tumor Characteristics	1-2	Tumor Stage	AJCC_GRP	1 = Stage I, 1A = Stage IA, 1B = Stage IB, 2A = Stage IIA, 2B = Stage IIB, 3A = Stage IIIA, 3B = Stage IIIB, 4 = Stage IV, 88 = Not applicable, 99 = Unknown	Med Rec Abs	FOR SAMPLE SPECIFICATION: Stage 1=1-1B, Stage 2=2A-2B
	1-2	ER Status	ER_STS	Negative, Weak Positive/Borderline, Positive	Path	FOR SAMPLE SPECIFICATION: : Pos=weak/borderline & positive Neg= Negative
	1-2	HER2 Status	HER2_STS	Negative, Weak Positive/Borderline, Positive	Path	Binary: Pos=weak/borderline & positive Neg= Negative
Stratification	1	Nodal Status	NODESTAT	1=Positive, 0=Negative	MA_VARS	STRATIFICATION: Binary: N0=negative, remainder positive
Variables used to account for complex survey design						
Study Design	1-2	Strata	STRATA	Non-Black age <50, Non-Black age 50+, Black age <50, Black age 50+	Survey	Categorical

	1-2	Sampling Weights	WT		Survey	Continuous
	1-2	Physician ID	NUM_PHYSICIAN	Physician Codes	Path	String

Med Rec Abs= Medical Record Abstraction Form, Path=Medical Abstraction Pathology Form

Aim 3 Methodology

General Approach

Patient, provider, and health system characteristics likely influence the uptake of ODX testing in breast cancer care.[28] While Aims 1 and 2 focused on patient-level factors obtained in CBCS-III, Aim 3 focused on provider and health system level factors that affect ODX recommendations and treatment decision-making. Specifically, to complement analyses of secondary datasets, Aim 3 used qualitative methods that provide a deeper understanding of factors influencing ODX testing practices. The objective of this aim was to identify oncologist-reported barriers and facilitators for ODX test uptake in clinical practice. I tested the working hypothesis that organizational facilitators, provider characteristics, attitudes towards ODX and social usage are associated with ODX test uptake. To this end, my approach involved semi-structured phone interviews with oncologists sampled across a range of health care settings in NC. The rationale for this aim was to elucidate factors that (1) influence ODX uptake and (2) have been understudied due to limitations in large secondary datasets. My expectation was that this research would contribute to indentifying factors that can be leveraged by policymakers to improve ODX test uptake, achieving the overall goal of this study.

Conceptual Model: Individual Acceptance of an Innovation

Aims 1 and 2 examined the influence of population characteristics on health services use. Aim 3 complements Aims 1 and 2 by exploring the influence of the environment. (Figure 2)

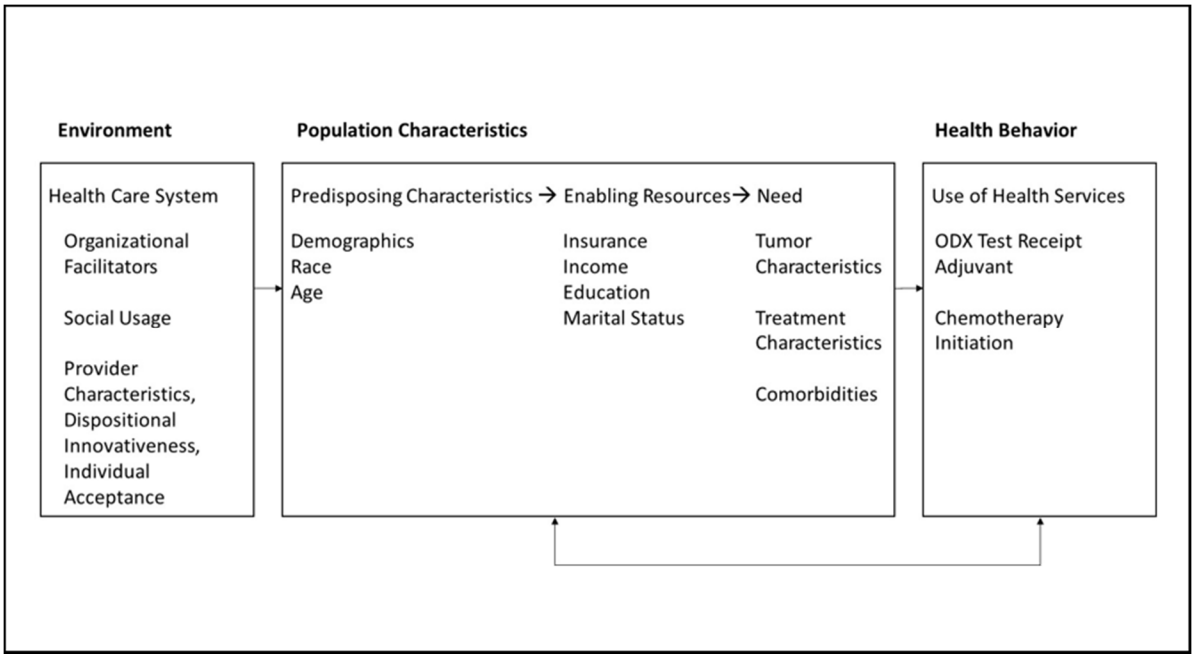

Figure 2. Andersen's Behavioral Model (adapted) describes how environmental factors, including health system factors influence health services use [1] (Aim 3)).

The environment can be studied using Frambach and Schillewaert's conceptual model. (Figure 3) In this study-context, individual acceptance of an innovation is equivalent to the recommendation of ODX testing for a patient[29]. Thus, it is important to understand a provider's level of acceptance for ODX testing, as this describes whether a provider has adopted an innovation and will recommend it to his or her patients [30]. According to Frambach and Schillewaert's conceptual model, individual acceptance is driven by organizational characteristics (e.g., organizational facilitators), provider characteristics (e.g., demographics), attitudes (e.g., beliefs about ODX), and social networks (e.g., peer usage of the test) (Figure 2). These represent organizational, interpersonal and intrapersonal level factors. For example, providers who believe that ODX testing is effective and informative for clinical decision-making have a higher likelihood of recommending ODX testing for a patient and using the test results in clinical decision-making. If a large proportion of the provider's colleagues are actively using ODX test results, the provider may be more likely to use the test as well. Similarly, if the organization in which the provider works has had training or support for ordering the ODX test, then the provider may be more likely to recommend ODX testing for his or her patients. This conceptual model drives the approach (specifically, the semi-structured interview guide) in Aim #3, which not only

sought to understand why and when this test is used, but also how this test is being used.

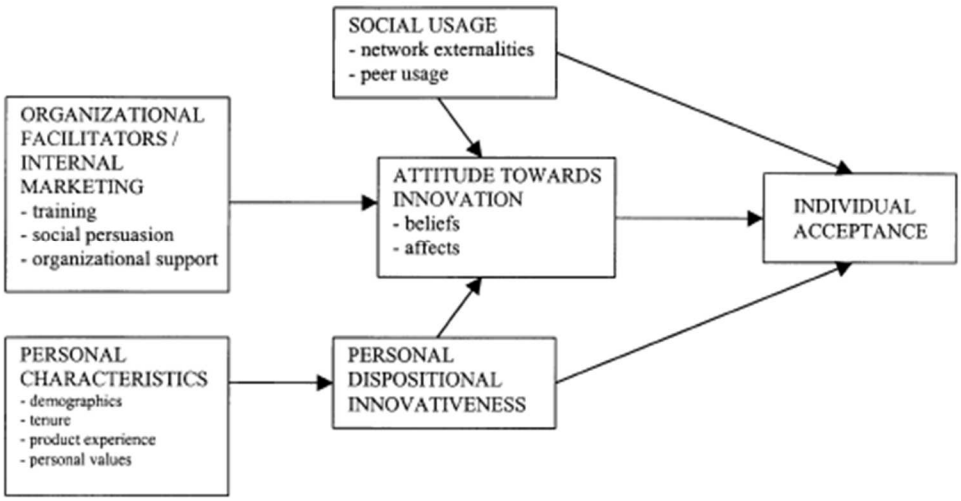

Figure 3. Provider acceptance of ODX test [29]

Table 2. Characteristics from the Electronic Provider Survey.

Variable		Variable Type	Categories	Source
Provider	**Attitude Towards the Innovation**	Qualitative	NA	Interview
	Dispositional Innovativeness	Categorical	strongly disagree, disagree, neutral, agree, strongly agree	Provider Survey
	Provider Characteristics			
	Gender	Binary	Male/Female	Provider Survey
	Age	Categorical	18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80 or older	Provider Survey
	Race	Categorical	White, Black, Asian, Hispanic, Native American, Other	Provider Survey
	Role in patient care	Binary	Surgical/Medical Oncology	Provider Survey
	Years since completing Training	Count	0-40	Provider Survey
Health Organization	**Social Usage**	Qualitative	NA	Interview
	Attitude Towards the Innovation	Qualitative	NA	Interview
	Organizational Characteristics			
	Public	Binary	Public/Private	Provider Survey
	Academic	Binary	Academic/Non-Academic	Provider Survey
	Urban	Categorical	Urban/Suburban/Rural	Provider Survey
	# providers in practice	Count	0-100	Provider Survey
	% breast cancer care in practice	Continuous	0-100	Provider Survey
	% breast cancer patients per provider	Continuous	0-100	Provider Survey
	# patients per week	Count	0-100	Provider Survey

	% ER/PR+ patients	Continuous	0-100	Provider Survey
	# patients per week	Count	0-100	Provider Survey
	Patient mix			
	% patients on Medicaid	Count	0-100	Provider Survey
	% Black patients	Count	0-100	Provider Survey
	Individual Acceptance	Qualitative and Count	How many times have you ordered ODX in the past month?	Provider Survey and Interview

Data Source/Eligibility Criteria

Data were obtained through semi-structured interviews with oncologists in North Carolina who see at least five breast cancer patients (to establish care, undergo treatment, for follow-up, etc). Because the ODX test can be ordered and reimbursed by both medical and surgical oncologists, we interviewed both types of breast oncologists. No additional eligibility criteria were applied to the sample population. In addition to obtaining qualitative data through interviews, all participants completed a brief survey prior to the interview.

Procedures

To achieve this aim, I conducted 30-minute phone interviews with up to 20 oncologists. The interview guides were semi-structured and focused on factors that are associated with provider acceptance and use of ODX testing in clinical practice (Table 2) (Figure 3). I elicited participants' beliefs and attitudes towards ODX as these perceptions likely influence a provider's recommendation for ODX, as well as how the ODX test result is used during adjuvant chemotherapy decision-making.

Recruitment

Oncologists were sampled across a diversity of health care settings (e.g., urban and rural, academic and non-academic, inpatient and outpatient clinics etc.) in North Carolina until theme

saturation was reached. Oncologists were identified through the NC licensure and North Carolina Oncology Association websites. Following identification, we sent a letter (via email or fax) to the oncologists. [Appendix 2] Providers who were interested in participating contacted me via email. All providers who were interested in participating were given a written informed consent and survey by email using Qualtrics software (Provo, UT) prior to the phone interview.[31] Completion of the informed consent and survey served as the formal enrollment mechanism for participants. [Appendix 3] Providers were compensated with a $100 VISA gift card for their participation in the survey and interview. (This was funded through Cancer Control Education Program research funds (R25-CA57726).

Data Collection Protocol

Survey data were maintained using Qualtrics software (Provo, UT). Data were stored without provider identifiers. 30-minute phone interviews were conducted on a secured conference call line with audio recording capabilities using FreeConferenceCall.com.[32] Two researchers, Megan Roberts (MCR) and Amy Bryson (AB) conducted the interviews with a semi-structured interview guide [Appendix 4]; MCR conducted the interviews and AB took notes and identified recurring themes for probing and establishing saturation of themes. A transcriptionist transcribed all audio files such that no identifying information was included in the text for analysis. Data analyses were ongoing, and provider recruitment ended upon saturation of themes. All identifying provider information was kept in a separate file from the interview and survey data. Data were stored on a password-protected computer.

Analysis

Template analysis was used to analyze qualitative data.[33] This analysis method has previously been applied to health services research.[34-38] Template analysis is a qualitative analysis technique, which involves developing a coding ‘template’ that includes hierarchical coding to summarize themes, which are identified a priori and modified throughout data analysis. This method incorporates both deductive and inductive approaches, as it recognizes that research design often employs a conceptual framework. Thus, a purely inductive approach, such as grounded theory, is not appropriate. Template analysis uses a priori codes, however these codes may be modified,

dispensed or added to in order to create a template to serve as the basis for data interpretation.[33] Following Frambach and Schillewaert's conceptual framework (Figure 2), organizational facilitators, provider characteristics, attitudes towards the innovation, social usage, and personal dispositional innovativeness were used as deductive, a priori codes. However an inductive approach was also used, and emergent codes were added to the analytical template (i.e., code book) as data analysis progressed. Furthermore, a priori codes were modified and dispensed as necessary.

Implementation of template analysis involved several steps. First, the initial coding template was based off of a subset of provider interviews (n=5). First transcripts were transcribed and reviewed by two coders (MCR and AB). Next the initial template (i.e., codebook) was employed using only a priori codes from the conceptual framework. During this initial coding, a priori codes were modified, dispensed and augmented with inductive codes. This initial code list represented our initial template for the codebook. Codes were organized in a hierarchal fashion, and a final template was created that included both inductive and deductive codes. This final template was then used to analyze all transcripts, which were double coded (MCR and AB). Coding was conducted using Atlas.ti.[39] Coders checked for consistency in applying the coding template to the transcribed interviews through discussion and reconciliation for a subset of interviews (n=5). Once consistency was established, double coding was conducted and the coders' analytic files were merged using Atlas.ti. Analysis was synthesized by organizational, interpersonal and intrapersonal level themes (Figure 4).

Expected Outcomes

The expected outcomes for this aim were to identify organizational and provider factors that are associated with ODX test uptake and to better understand how the test is being used in adjuvant chemotherapy decision-making. This expected outcome attains this aim's objective of identifying factors that influence ODX uptake and subsequent adjuvant chemotherapy use. This helps attain this dissertation's overall goal, as the outcomes elucidated modifiable factors that can be targeted in future interventions aimed at increasing ODX test uptake.

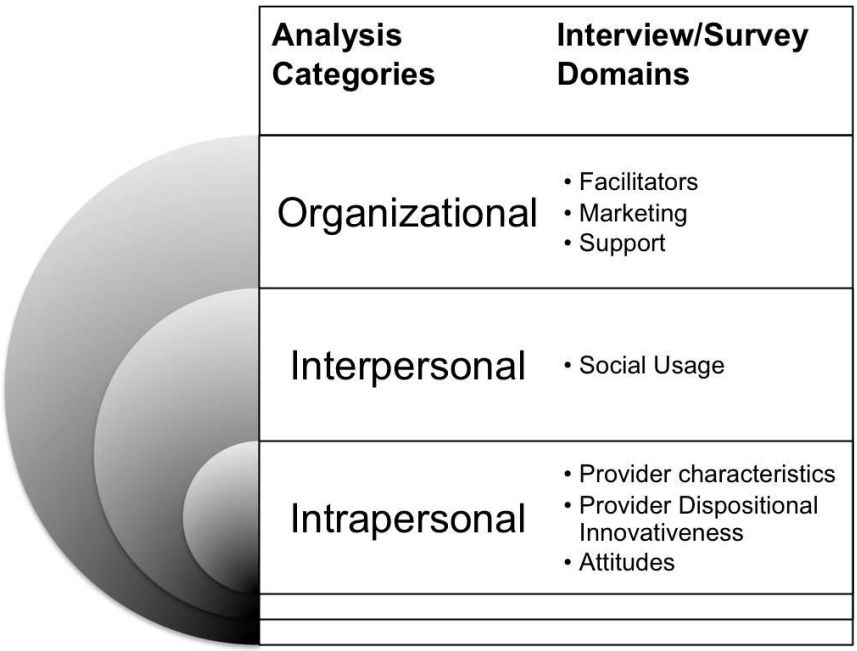

Figure 4. Conceptual model based on Frambach and Schillewaert

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CHAPTER 4. RACIAL VARIATION IN THE UPTAKE OF ONCOTYPE DX FOR EARLY STAGE BREAST CANCER

Background

This year, an estimated 231,840 women will be diagnosed with invasive breast cancer [1], almost half with early stage, hormone receptor positive breast cancer [2, 3]. Among these women, some will reap benefit from chemotherapy in addition to endocrine therapy as part of their adjuvant therapy. Historically, clinicopathological features, such as tumor grade, size, age and comorbidities, drove adjuvant chemotherapy decision-making [4, 5]; however, commercially available genetic technologies, such as Oncotype DX (ODX), alleviate some of the remaining uncertainty associated with using only clinicopathological criteria to estimate adjuvant chemotherapy benefit.

ODX became commercially available in 2004 for the management of early stage, node negative, estrogen receptor positive (ER+) breast cancer [6]. The test is a 21-tumor gene expression profiling panel that categorizes women into three risk groups (i.e., low, intermediate, high) based on 10-year risk of distant recurrence [7]. Women with low risk scores are unlikely to benefit from the addition of chemotherapy to adjuvant endocrine therapy, whereas those with high scores derive considerably more benefit [7]. Evidence suggests that providers change adjuvant chemotherapy decision-making in about 30%-40% of patients in the presence of ODX results [8-12], reducing the overuse of adjuvant chemotherapy [5, 13]. Furthermore, this test appears to be cost-effective [5, 14, 15]. Level I evidence of chemotherapy decision-making based on ODX in node-negative, ER+ disease awaits the results of the randomized TAILORx trial [16].

The first private insurer began covering ODX for women with ER+, human epidermal growth factor receptor 2 negative (HER2-), early stage breast cancer in 2005 [6]. Medicare also began covering ODX testing for this patient group in 2006 [6]. Soon thereafter, medical guidelines began incorporating the use of ODX for adjuvant chemotherapy decision-making among node negative breast cancer patients with ER+, HER2-, and early stage (stage I-II) disease with tumors $\geq$ 0.5cm [6]. Since the initial validation of ODX in node negative patients, several studies have demonstrated the

prognostic validity of ODX for women with 1-3 positive nodes as well [17-19]. The RxPONDER trial, is underway to verify observational findings and evaluate ODX for women with early stage, node positive, ER+ breast cancer [20]. Currently, ODX testing for women with positive lymph nodes is not guideline recommended or widely covered by insurance.

By helping clinicians make individualized evidence-based decisions regarding chemotherapy, ODX testing can contribute to targeted, high quality care for women with breast cancer. However, there also remains the potential for unintended consequences: If technologies, such as ODX, are not equally accessed by patients, they may exacerbate existing disparities in breast cancer care processes and outcomes [21]. Among guideline-eligible (i.e., node negative, ER+, stages I-II) patients, only 10-50% are receiving ODX testing [22, 23]. Understanding who has access to ODX testing will be important in targeting interventions to improve access to such technologies. The few studies that have examined the effect of race on ODX testing offer mixed evidence on racial disparities in testing uptake [22-26]; notably, these studies have limited generalizability as they have been conducted in academic settings [22, 24], hospitals within a single urban setting [22, 23], or among women with Medicare [26].

We now seek to extend prior research by explicitly examining whether ODX use varies by race across diverse health care settings. Furthermore, we sought to disentangle the effect of race on ODX test use by lymph node status, as clinical guidelines and insurance guidelines for ODX testing vary among these two patient groups.

Methods

Data Source

The Carolina Breast Cancer Study (CBCS-III) (NIH 8389741) is a population-based study of women diagnosed with breast cancer across 44 counties in North Carolina between 2008 and 2013.. CBCS-III is among the largest cohort studies of breast cancer in Black women in the United States. Because it oversampled Black women, CBCS-III is particularly well-powered to examine racial health disparities in breast cancer. Between 2008 and 2013, CBCS-III enrolled 2,998 women, 20-74 years old with invasive breast cancer through rapid case ascertainment in collaboration with the North Carolina Cancer registry. Patients were sampled by randomized recruitment in four strata: Black

women < 50 years old, Black women ≥ 50 years, non-Black women < 50 years old, and non-Black women ≥ 50 years. For this study, we used baseline survey, medical record abstraction, and pathology report abstraction data.

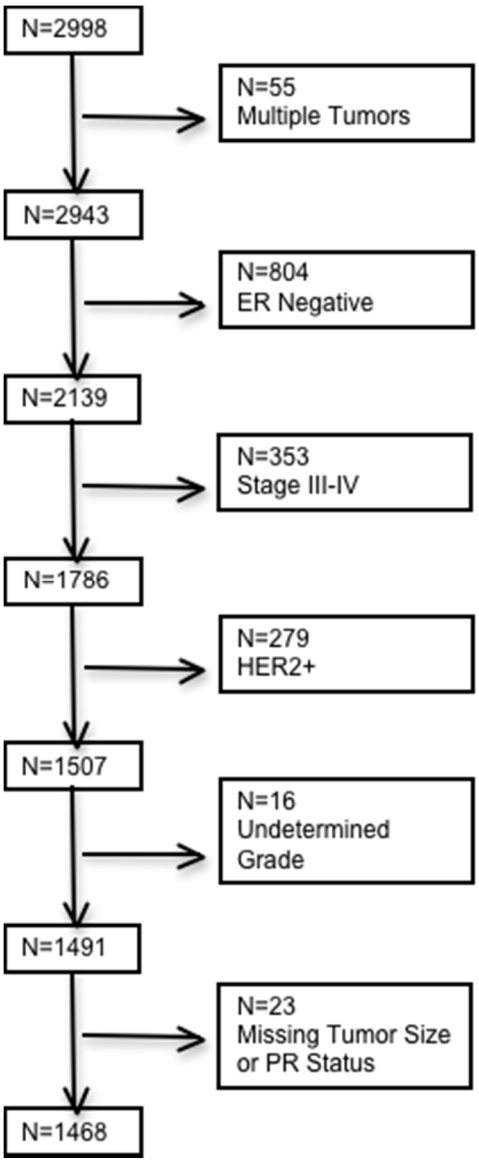

Figure 5. Sample population with exclusion criteria

Subjects

We included women whose breast cancer was: (1) ER+, (2) stage I-II, and (3) HER2-. Patients were further excluded patients if they had multiple tumors or undetermined tumor grade,

tumor size or progesterone receptor (PR) status (Figure 5). There were no significant differences in missing tumor data by race: 1.5% of Black had missing tumor information compared to 2.1% of non-Black women (p=0.51). Our sample size calculations suggested that we would be able to detect crude effect sizes of 10% with 80% power.

Measures

We used the IOM's definition of health disparity: "the difference in treatment or access not justified by the differences in health status or preferences of the groups." This definition implies that race is a social construct, thus controlling for socioeconomic variables that are associated with race may mask existing racial disparities [27] [28]. As such, socioeconomic variables (i.e., marital status, education, current employment (since diagnosis), family income, and insurance type) were not included in our primary model, which measured the reduced form effect of race on ODX testing. In order to observe the residual direct effect of race on ODX testing, we also developed a secondary model, which included socioeconomic status (SES) covariates, providing insight into contributing factors for racial disparities.

Dependent variable: Our dependent variable, ODX testing, was abstracted from pathology reports. Patients without ODX reports in their pathology records were assumed not to have received the test.

Independent variable**:** Race, abstracted from the baseline survey, was patient self-reported. Race was dichotomized as "non-Black" including White, Asian and other race, or "Black", irrespective of ethnicity.

Covariates**:** Covariates included tumor (i.e., tumor stage, tumor size, tumor grade, and PR status), treatment (i.e., lumpectomy vs. mastectomy, radiation), and clinical characteristics (i.e., comorbidities and age). Age at diagnosis was dichotomized (< 50 versus $\geq$50 years old). Using comorbidities from baseline surveys, we calculated a count of comorbidities from five clinical categories: heart disease, hypertension, obesity, diabetes, and chronic obstructive pulmonary disease. Tumor and treatment characteristics were abstracted from the pathology report and medical reports, respectively. Tumor stage and radiation therapy were dropped due to multicollinearity with tumor size and surgery type, respectively. Endocrine therapy and adjuvant chemotherapy, which

were derived from the medical record abstraction, were each dichotomized as “ever starting therapy”. Adjuvant chemotherapy was defined as chemotherapy occurring after the first primary surgery (i.e., lumpectomy or mastectomy). Our secondary model also included socioeconomic variables, including marital status (i.e., married or living as married vs. other), education (i.e., less than high school, high school, or college and more), current employment since diagnosis (i.e., yes, no, not reported), family income (i.e., <15K, 15-30K, 30-50K, >50K per year, not reported), and insurance type (i.e., Medicaid, Medicare, private, and/or uninsured).

Analyses

Descriptive statistics were calculated using population weights. We compared characteristics between Black and non-Black women, as well as those who did and did not receive ODX testing, using weighted linear regression for continuous variables and weighted chi-square tests for binary/categorical variables. For our multivariate analyses, we employed generalized linear models (GLM) with the Poisson family and log link to examine the association between race and ODX use. Modified Poisson regression with sandwich error terms estimates relative risk consistently and efficiently with correlated binary outcomes [29, 30]. Both descriptive and multivariate analyses addressed complex survey design through sample weights and design effects using Taylor Series Approximations: We also accounted for clustering at the provider level. Analyses were conducted using STATA software (StataCorps, College Station, TX).

Because factors that influence ODX testing may vary between women with lymph node positive verses lymph node negative breast cancer, we conducted sensitivity analyses. This uncovered a need to stratify analyses by lymph node status (N0 vs. N1). Thus, we present six models: crude, primary, and secondary models within each lymph node stratum.

Results

Characteristics of patients by race and ODX uptake: Overall, non-Black women tended to have smaller, lower grade, and progesterone receptor positive tumors), fewer comorbidities, older age at diagnosis, and higher SES compared to Black women (Table 3). ODX use varied by race, with fewer Black women receiving ODX compared to non-Black women (33.9% vs. 43.2%, p=0.001).

However, upon stratifying the descriptive analysis by node status, this racial difference in ODX test receipt was only present among the node positive patients (14.4% vs. 34.0%, p<0.001).

Less than half of women who met criteria for ODX testing had ODX results reported in their pathology report. Node positive patients were less likely to receive ODX testing compared to node negative patients (30% vs. 45%, p=0.001), however this difference appears to diminish over time (Figure 6). Rates of ODX testing increased among node positive women in 2012/2013 compared to 2008, while staying relatively stable in among node positive patients: Interestingly, rates of ODX testing among both sub-populations appear to be similar after 2008 (Figure 6). Patients receiving ODX testing tended to be younger, have fewer comorbidities, and have moderate tumor size and grade compared to patients who did not receive the test. Those receiving ODX were more likely to also receive adjuvant chemotherapy compared to those who did not receive ODX testing, and both groups were equally likely to initiate endocrine therapy (Table 4).

Table 3. Population-Weighted, Sample Characteristics (Mean with Standard Error/Proportion) by Race and Lymph Node Status

		FULL SAMPLE			NODE POSITIVE			NODE NEGATIVE		
		Non-Black N = 859 Wgt. N = 3,895	Black N = 609 Wgt. N = 793	p	Non-Black N = 203 Wgt. N = 828	Black N = 180 Wgt. N = 218	p	Non-Black N = 656 Wgt. N = 3,067	Black N = 429 Wgt. N = 574	p
ODX	ODX Assay included?	43.2	33.9	0.001	34	14.4	<0.001	45.7	41.4	0.23
	ODX Recurrence Score	17.7 (8.3)	19.0 (16.2)	0.17	18.0 (6.4)	19.2 (13.9)	0.61	17.7 (8.7)	19.0 (16.7)	0.20
Tumor Characteristics	Stage 1 (v. 2)	65.9	55.3	<0.001	11.6	7.0	0.16	80.6	73.7	0.02
	Tumor size category			<0.001			0.22			0.01
	<2 cm	75.5	65.9		54.8	45.5		81.0	73.7	
	2-5 cm	22.4	32.3		43.5	53.3		16.8	24.3	
	>5 cm	2.1	1.8		1.7	1.2		2.2	2.0	
	Grade			<0.001			0.003			0.004
	1	38.4	27.9		29.5	18.2		40.8	31.6	
	2	46.0	47.2		48.8	43.8		45.2	48.5	
	3	15.6	24.9		21.7	38.0		13.9	20.0	
	PR Positive	89.9	80.8	<0.001	92.5	80.2	0.004	89.2	81.0	<0.001
Treatment Characteristics	ET Initiation	90.7	87.1	0.06	93.7	88.2	0.08	89.8	86.7	0.15
	Adjuvant Chemotherapy Initiation	27.5	36.7	<0.001	56.6	66.1	0.09	19.6	25.5	0.03
	Radiation	68.1	68.0	0.97	71.3	76.3	0.30	67.3	64.9	0.49
	Lumpectomy (v. Mastectomy)	62.9	61.9		49.4	49.2	0.97	66.5	66.7	0.13
Clinical Characteristics	Age at diagnosis	57.7 (8.7)	55.5 (16.9)	0.003	56.0 (9.2)	52.6 (15.0)	<0.001	58.2 (8.6)	56.6 (17.2)	0.04
	Diagnosis Year			0.49			0.41			0.49
	2008	11.2	10.9		14.8	14.5		10.2	9.6	
	2009	19.4	19.2		15.7	22.6		20.4	17.9	
	2010	24.3	23.0		19.9	19.7		25.5	24.3	
	2011	23.7	28.0		26.4	27.3		23.0	28.3	
	2012/2013	21.4	18.8		23.2	12.2		20.9	20.0	
	Comorbidities									
	Diabetes	11.0	25.7	<0.001	12.5	20.8	0.06	10.6	27.6	<0.001

	COPD	3.6	3.4	0.87	3.8	3.2	0.77	3.6	3.5	0.97
	Obesity	11.0	21.9	<0.001	10.0	19.5	0.02	11.3	22.8	<0.001
	Heart disease	6.7	7.2	0.73	7.8	5.5	0.43	6.4	7.9	0.41
	Hypertension	38.9	65.7	<0.001	39.4	61.4	<0.001	38.8	67.3	<0.001
Socioeconomic Status Variables	Family Income			<0.001			<0.001			<0.001
	<15K	7.1	25.1		8.2	30.7		6.8	23.0	
	15-30K	12.3	25.0		9.4	29.6		13.1	23.3	
	30-50K	17.1	19.3		18.0	15.7		16.8	20.6	
	>50K	56.5	25.1		60.5	17.3		55.4	28.1	
	Not reported	7.0	5.4		3.9	6.7		7.9	4.9	
	Insurance									
	Private	78.9	63.7	<0.001	78.7	57.2	<0.001	79.0	66.0	<0.001
	Medicaid	6.0	23.5	<0.001	6.9	28.9	<0.001	5.8	21.6	<0.001
	Medicare	35.4	37.4	0.51	28.7	32.8	0.47	37.2	39.1	0.61
	Uninsured	2.9	9.7	<0.001	2.5	14.8	<0.001	3	7.7	0.001
	Married	71.1	39.4	<0.001	73.8	34.2	<0.001	70.3	41.4	<0.001
	Employed			0.12			0.16			0.35
	Unemployed	53.9	58.7		50.9	61.2		54.7	57.7	
	Employed	45.4	39.9		47.7	36.8		44.8	41.1	
	Not reported	0.7	1.4		1.4	2.0		0.5	1.2	
	Education			<0.001			<0.001			<0.001
	HS & Post HS	49.0	55.9		39.0	60.9		51.7	54.0	
	College+	44.8	30.6		50.4	26.9		43.3	32.0	
	<HS	6.1	13.5		10.6	12.2		4.9	14.0	

Table 4. Sample Characteristics (Mean with Standard Error/Proportion) by ODX Use and Lymph Node Status.

		FULL SAMPLE			NODE POSITIVE			NODE NEGATIVE		
	ODX Test Receipt	No ODX	ODX		No ODX	ODX		No ODX	ODX	
	N	900	568	p	302	81	p	598	487	p
	Weighted N	2734	1953		734	313		2001	1640	
Tumor	Tumor Size			0.04			0.18			<0.001
	<2 cm	74	73.6		49.4	61.1		83.1	75.9	
	2-5 cm	22.9	25.8		48.7	38.1		13.5	23.4	
	>5 cm	3	0.7		2	0.8		3.4	0.7	
	Grade			0.003			0.03			<0.001
	1	40.7	31		26.6	28.4		45.9	31.5	
	2	41.3	53.1		43.2	58.4		40.6	52	
	3	18	16		30.2	13.2		13.5	16.5	
	PR Positive	86.5	91.1	0.03	89.7	90.4	0.86	85.3	91.2	0.01
Treatment	ET Initiation	87.1	94.1	<0.001	90.6	97	0.12	85.9	93.6	<0.001
	Adjuvant chemo	30.7	26.7	0.18	70.4	30.9	<0.001	16.1	25.9	<0.001
	Radiation	69.4	66.4	0.38	77.2	61.1	0.01	66.5	67.4	0.82
	Lumpectomy (v. Mastectomy)	38.7	35.4	0.43	55.8	38.6	0.01	32.4	34.8	0.56
Clinical	Age at diagnosis	57.6 (10.9)	56.9 (9.9)	0.28	54.0 (12.0)	58.3 (8.1)	0.004	58.9 (10.1)	56.6 (10.3)	0.002
	Diagnosis Year			>0.99			0.08			0.41
	2008	10.9	11.5		18.2	6.7		8.2	12.5	
	2009	19	19.8		17.6	16.1		19.5	20.5	
	2010	24.6	23.4		20.8	17.6		26	24.5	
	2011	24.6	24.3		25.7	28.5		24.1	23.5	
	2012/2013	20.9	21.0		17.2	29.8		21.9	18.9	
	Comorbidites									
	Diabetes	15.5	10.6	0.03	15.7	10.6	0.39	15.4	10.6	0.06
	COPD	4.9	1.8	0.01	5.3	0	0.08	4.8	2.1	0.05
	Obesity	13	12.6	0.86	14.3	6.5	0.12	12.5	13.8	0.59
	Heart Disease	8.9	3.9	0.005	8.5	4.8	0.4	9	3.7	0.008
	Hypertension	45.3	40.8	0.19	41.8	49.3	0.28	46.7	39.2	0.07

Socioeconomic	Family Income			<0.001			0.002			0.006
	<15K	12.2	7.2		15.9	6.1		10.9	7.4	
	15-30K	15.6	12.9		14.2	12.2		16.1	13	
	30-50K	17.4	17.6		21	9.4		16	19.2	
	>50K	46.2	58.1		43.2	70.7		47.3	55.7	
	Not Reported	8.6	4.1		5.7	1.7		9.7	4.6	
	Insurance									
	Private	74.6	79.1	0.13	72.8	79	0.39	75.3	79.1	0.26
	Medicaid	10.3	6.7	0.03	11.9	9.1	0.55	9.7	6.3	0.04
	Medicare	37.3	33.5	0.24	29	30.5	0.82	40.3	34.1	0.09
	Uninsured	4.7	3	0.06	6.1	2.7	0.08	4.2	3.1	0.3
	Married	62.7	70	0.02	62.1	73.6	0.06	62.8	69.3	0.06
	Employed			0.11			0.35			0.009
	Unemployed	57.4	50.9		53.1	53		59	50.5	
	Employed	41.7	48.5		46.1	43.8		40	49.3	
	Not Reported	0.9	0.7		0.8	3.2		1	0.2	
	Education			0.07			0.56			0.09
	HS & Post HS	51	49.1		41.8	47.9		54.4	49.3	
	College+	40.3	45.4		46.1	44.1		38.2	45.6	
	<HS	8.7	5.6		12.2	8		7.4	5.1	

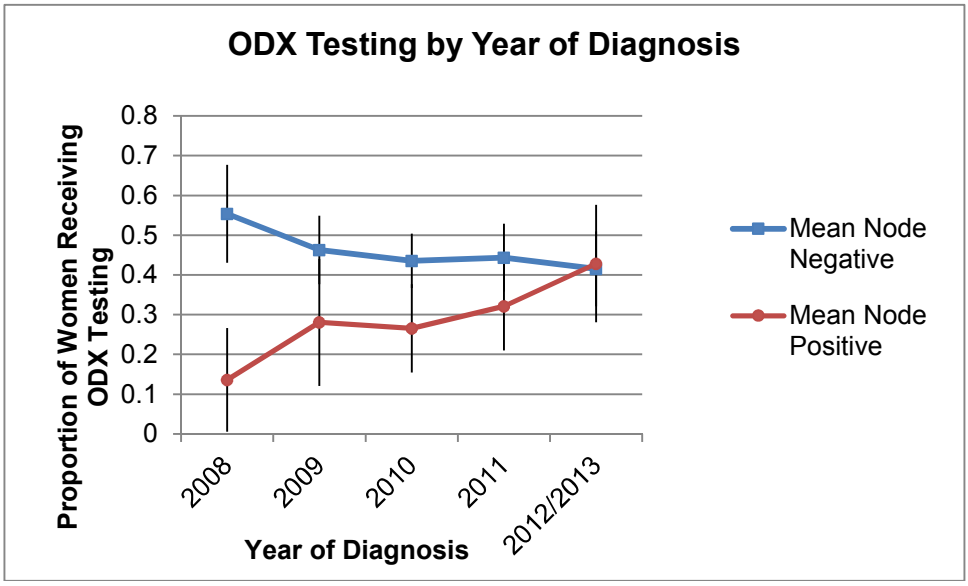

Figure 6. Proportion of ER+, HER2-, Stage I-II patients who had an ODX testing reported over time, by lymph node status (with population weights)

Race and other characteristics independently associated with receiving ODX test**:** Among node negative patients, race was not associated with receiving ODX testing, with similar results for the crude, primary and secondary models (Table 5). Tumor characteristics were independently associated with ODX test use: higher tumor grade, PR positivity, and moderate tumor size were associated with a greater likelihood of receiving ODX testing among node negative women. SES factors among node negative patients were not associated with ODX use. Year of diagnosis was not associated with receiving ODX testing among node negative women.

Table 5. Modified Poisson Regression Results of ODX Test Use for Node Negative Breast Cancer Patients

n=1049 PSU=455 Pop. Size=3641	**Crude Model** **RR**	**95% CI**	**p**	**Primary Model** **RR**	**95% CI**	**p**	**Secondary Model** **RR**	**95% CI**	**p**
Black **(v. non-**Black**)**	**0.90**	**0.77-1.067**	**0.23**	**0.91**	**0.76-1.094**	**0.33**	**0.95**	**0.78-1.15**	**0.58**
Tumor Size (v. <2cm)									
2-5 cm				1.30	1.083-1.56	0.005	1.31	1.10-1.56	0.003
>5 cm				0.31	0.089-1.045	0.059	0.31	0.091-1.019	0.054
Grade (v. 1)									
2				1.41	1.16-1.72	0.001	1.41	1.15-1.72	0.001
3				1.42	1.098-1.83	0.007	1.45	1.13-1.86	0.003
PR Positive (v. negative)				1.48	1.085-2.029	0.014	1.50	1.099-2.051	0.011
Mastectomy (v. lumpectomy)				1.031	0.86-1.23	0.74	1.05	0.88-1.25	0.58
# Comorbidities				0.91	0.83-1.011	0.080	0.95	0.86-1.060	0.38
< 50 Age at Diagnosis (v. >50)				1.13	0.95-1.33	0.16	1.074	0.90-1.28	0.42
Diagnosis Year (v. 2008)									
2009				0.86	0.66-1.12	0.26	0.84	0.65-1.10	0.22

2010				0.84	0.66-1.072	0.16	0.78	0.60-1.00	0.052
2011				0.85	0.66-1.10	0.23	0.8	0.62-1.038	0.093
2012/2013				0.79	0.58-1.074	0.13	0.74	0.54-1.011	0.058
Family Income (v. <15K)									
15-30K							0.97	0.66-1.43	0.89
30-50K							1.12	0.77-1.62	0.56
>50K							1.017	0.68-1.52	0.94
Not reported							0.64	0.39-1.069	0.088
Uninsured (v. insured)							0.84	0.55-1.28	0.42
Married (v. unmarried)							1.11	0.91-1.37	0.30
Employment (v. unemployed)									
Employed							1.068	0.89-1.29	0.48
Not reported							0.46	0.91-2.13	0.32
Education (v. HS/HS+)									
College or more							1.082	0.92-1.27	0.33
<HS							0.87	0.56-1.35	0.53
Constant	0.46	0.41-0.51	<0.001	0.30	0.19-0.47	<0.001	0.26	0.15-0.45	<0.001

Table 6. Modified Poisson Regression Results for the Association between Race and Covariates and ODX Testing in Node Positive Breast Cancer Patients

n=360 PSU=232 Pop. Size=1047	**Crude Model**			**Primary Model**			**Secondary Model**		
	RR	**95% CI**	**p**	**RR**	**95% CI**	**p**	**RR**	**95% CI**	**p**
Black **(v. non-**Black**)**	**0.42**	**0.27-0.66**	**<0.001**	**0.54**	**0.35-0.84**	**0.006**	**0.68**	**0.39-1.19**	**0.172**
Tumor Size (v. <2cm)									
2-5 cm				0.82	0.54-1.24	0.35	0.90	0.59-1.39	0.64
>5 cm				0.86	0.13-5.57	0.88	1.30	0.20-8.26	0.79
Grade (v. 1)									
2				1.19	0.77-1.83	0.44	1.24	0.76-2.035	0.39
3				0.57	0.26-1.24	0.16	0.56	0.27-1.16	0.12
PR Positive (v. negative)				1.022	0.60-1.75	0.94	1.083	0.58-2.026	0.80
Mastectomy (v. lumpectomy)				0.84	0.56-1.27	0.41	0.93	0.62-1.39	0.71
# Comorbidities				0.87	0.68-1.11	0.25	0.88	0.71-1.084	0.23
< 50 Age at Diagnosis (v. >50)				0.49	0.32-0.75	0.001	0.52	0.33-0.80	0.003
Year of Diagnosis (v. 2008)									
2009				2.40	0.85-6.75	0.097	1.99	0.71-5.55	0.19
2010				2.061	0.81-5.26	0.13	1.65	0.60-4.53	0.33

2011				2.53	0.97-6.56	0.057	2.00	0.80-5.015	0.14
2012/2013				3.17	1.15-8.76	0.026	3.10	1.088-8.86	0.034
Family Income (v. <15K)	.7								
15-30K							1.497 (0.790)		0.446
30-50K							0.952 (0.558)		0.934
>50K							2.516 (1.350)		0.087
Not reported							0.802 (0.791)		0.791
Uninsured (v. insured)							0.73	0.24-2.25	0.58
Married (v. unmarried)							0.93	0.59-1.48	0.77
Employment (v. unemployed)									
Employed							0.82	0.53-1.25	0.35
NA							3.53	1.37-9.10	0.009
Education (v. HS-Post HS)									
College or more							0.62	0.40-0.96	0.031
<HS							0.74	0.27-2.033	0.56
Constant	0.34	0.27-0.43	<0.001	0.22	0.071-0.71	0.011	0.16	0.032-0.83	0.029

Among node positive patients, Black women were significantly less likely to receive ODX testing on their tumor compared to non-Black women (adjusted RR (aRR): 0.54, 95%CI:0.35-0.84, p=0.006) (Table 6). Furthermore, women under the age of 50 with positive nodes were significantly less likely to receive ODX testing compared to women over the age of 50 years, holding other factors constant (aRR=0.49, 95%CI: 0.32-0.75, p=0.001; aRR=0.052, 95%CI: 0.33-0.80, p=0.003). Women were significantly more likely to receive ODX in 2012-2013 compared to 2008, holding other factors constant (aRR=3.2, 95%CI: 1.15-8.76, p=0.03; aRR=3.1, 95%CI: 1.37-9.10, p=0.009). These findings were consistent across models: However, race was not statistically associated with receiving ODX testing in our secondary model, controlling for other factors, including SES variables (aRR=0.68, 95%CI: 0.39-1.19, p=0.172).

Discussion

In North Carolina between 2008 and 2013, less than half of women who were eligible for ODX testing (those with early stage, ER+, HER2-, node negative breast cancer) received ODX testing, and about one third of women with node positive breast cancer received ODX testing. However, these patterns changed over the course of the study, with increasing uptake of ODX testing among node positive patients in later years. Nonetheless, our findings corroborate a previous study (conducted between 2009-2010) demonstrating a lack of racial disparities in node negative women [24]. Because ODX is also commonly used in node positive women it is important to study uptake of the test in this group of women; to our knowledge, to our knowledge, our study is the first to describe racial disparities in ODX test use among a subgroup of node positive women.

Overall, Black women in the study cohort were more likely to initiate adjuvant chemotherapy compared to non-Black women. This is likely because Black women experienced larger, higher grade breast cancers compared to non-Black women, consistent with previous work in the Carolina Breast Cancer Study, Phase 1 and 2 [31]. Among node-negative patients, adjuvant chemotherapy initiation was higher among those who received ODX testing than those who did not; notably, this pattern was reversed among node-positive patients. Evidence suggests that among node negative women, patients are less likely to receive ODX testing if they have preferences against adjuvant chemotherapy, as the ODX test result may not influence the treatment decision-making process [32,

33]. However among node positive patients, ODX testing may be more commonly offered to women for whom providers wish to forgo chemotherapy [33], potentially explaining different chemotherapy initiation patterns by node status. Studies examining the cost effectiveness of ODX should stratify analyses by nodal status, as different patterns of ODX and adjuvant chemotherapy use may occur across these strata.

ODX Use for Node Negative Patients

Tumor characteristics were associated with ODX use among women with node negative disease. Moderate tumor size, moderate/higher tumor grade, and PR positivity were associated with an increased likelihood of receiving ODX testing. These results suggest that, among eligible women, there is a subgroup of women with medium size and/or grade tumors for whom chemotherapy decision-making is more difficult, and in whom the additional information from ODX testing may be helpful. A prior study by DeFrank et al., suggested that in cases of uncertainty, ODX may offer an extra piece of information to make decisions about forgoing chemotherapy [24]. Perhaps patients with especially favorable or unfavorable tumor characteristics were more likely to forgo ODX testing, because the patient and provider already had enough information to make an informed adjuvant chemotherapy decision, even in the absence of the ODX risk score.

We did not find racial or SES differences in ODX test receipt among node negative patients. Perhaps this is due to wide coverage and availability of ODX testing for node negative breast cancer [6]. For eligible women who are uninsured or lack adequate coverage for ODX, Genomic Health (the makers of ODX) provides a financial assistance program [34]. This reduces financial barriers to access this test and may partially explain why race and SES are not associated with ODX use among node negative patients.

ODX Use for Node Positive Patients

In contrast, our findings suggest a racial difference in ODX test receipt among node positive women. Specifically, Black women were significantly less likely to receive ODX compared to non-Black women. In sensitivity analyses, this effect persisted across year of breast cancer diagnosis (data not shown). Unlike ODX testing among node negative patients, ODX testing for node positive patients is not generally covered by Medicare or commercial insurers, as the test is not yet guideline-

recommended in the node positive setting. Because ODX is not widely covered for node positive women, concerns about perceived costs may act as a barrier to receiving ODX, despite Genomic Health providing financial assistance. Because SES and race are correlated, perceived costs could explain potential racial differences in receiving ODX testing. This may partially explain the observed attenuated association of race with ODX test receipt in the secondary model, which included SES covariates.

Additionally, a qualitative study indicated that North Carolina providers are primarily ordering ODX among node positive patients within the context of the ongoing Southwest Oncology Group (SWOG) RxPONDER trial (S1007) [33]. Thus, low recruitment of Black women into this clinical trial may be a contributing factor for racial differences in this group, as a large body of evidence has demonstrated that Black women are less likely to enroll in clinical trials compared to Non-Black women [35, 36]. Future studies should test whether there is an association between race, trial participation, and access to new genetic technologies.

Current medical guidelines do not recommend ODX use in this node positive subgroup of early stage, ER+ breast cancer patients. Thus, while Black women in our sample are less likely to receive ODX testing, they are actually receiving more guideline concordant care compared to non-Black with node positive breast cancer. For this reason, differential receipt of ODX testing does not necessarily reflect a racial disparity in the quality of care. This paradox illustrates challenges that will accompany measuring disparities in the early adoption of new genetic technologies into clinical practice moving forward.

In addition to racial differences, women younger than 50 were less likely to receive ODX testing compared to those older than 50 years in the node positive group. Because younger women tend to be healthier and thus, tolerate chemotherapy better, it is possible that providers are more likely to move forward with chemotherapy according to guidelines [33, 37]. Alternatively, providers may be more likely to order ODX testing for older adults to justify not giving adjuvant chemotherapy to those who are frail or experiencing multiple comorbidities.

Finally, year of breast cancer diagnosis was strongly correlated with likelihood of ODX testing patterns in node positive women. This is likely due to accruing evidence for ODX testing among these

patients over time. The first major studies suggesting ODX's prognostic validity in node positive patients were reported in 2008 among women receiving chemotherapy and endocrine therapy [19], and 2010 among women receiving endocrine therapy alone [17, 18]. In 2010, a randomized study demonstrated ODX testing's predictive validity among post-menopausal women with node positive breast cancer (16). Thus, mounting evidence beginning in 2008 may explain why year of diagnosis was a strong predictor of receiving ODX testing in node positive women. Notably, we do not see this trend in node negative patients, as ODX testing had already been added to clinical guidelines by 2008 for these patients [6].

Limitations

This study has several limitations. First, we were unable to account for patient preferences, which likely play a large role in ODX testing and adjuvant chemotherapy decisions. Evidence suggests that preferences around treatment for early stage breast cancer may differ by race [38]. If so, patient preferences may be a mediating variable between race and ODX use. Second, ODX use was determined through pathology report abstraction. It is possible that patients received ODX testing, but this information was not added to medical and pathology records. However, our rates of ODX uptake were similar to those reported in other studies and increased over time [22, 23]. Any data missing on ODX uptake is likely to be missing at random; if so, the effect of exposure misclassification would likely be non-differential. Third, our study was powered to observe 10% crude racial differences: however with the inclusion of covariates our models, in particular secondary models, were underpowered. Notably, with its oversampling of Black women, CBCS III presented the best opportunity currently available to examine racial disparities surrounding ODX test uptake. Fourth, our models did not include organizational or provider level characteristics that influence ODX use. Two studies indicate that organizational level factors, such as being seen at a tertiary medical center [23] or a community cancer center (versus a comprehensive cancer center)[25] may decrease the likelihood of receiving ODX testing. Of these studies, one found that being seen at a tertiary medical center explained racial differences in the uptake of ODX testing. Planned data linkages will facilitate exploring multilevel factors in the future. Finally, the inclusion of SES required redefining family income to include a "not reported" category: this demonstrates the challenges of measuring the

independent effects of SES, as non-random underreporting of these variables is common and may result in biased estimates [39].

Conclusions

Overall this study contributes to our understanding of racial variation in ODX test uptake, particularly by describing these differences across lymph node status. Racial disparities were not observed among women with node negative disease for whom ODX testing is guideline recommended and widely covered by insurance. This is heartening as more genetic technologies are incorporated into clinical guidelines for the care of cancer. Conversely, the observed racial difference in node positive patients suggests that newer applications of genetic technologies may be used less by racial minorities. This may occur for several reasons: (1) lower uptake of newer applications of technologies because of disparities in clinical trial participation, (2) less insurance coverage, or (3) unexplained provider and organizational differences in genetic technology use where racial minorities access care. Future studies should examine these factors' association with ODX testing explicitly. Because ODX testing in node positive patients is currently not included in clinical guidelines, this racial difference does not describe a disparity. However, this poses an important question as we move into the era of "precision medicine:" How we will measure disparities in access to the latest advances in genetic technologies for cancer care? Moving forward, we should consider this question as we work to ensure that newer applications of genetic technologies are accessible to all patients who may benefit from the test.

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CHAPTER 5. RACIAL VARIATION IN ADJUVANT CHEMOTHERAPY INITIATION FOR BREAST CANCER PATIENTS RECEIVING ONCOTYPE DX TESTING

Background

Black women are less likely to develop, but more likely to die from, breast cancer compared to non-Black women [1]. This disparity likely arises from a complex array of biological, societal and health system factors, including access to high quality cancer care [2]. For example, Black women with breast cancer are less likely to receive guideline concordant cancer treatment, with mixed evidence about adjuvant chemotherapy [3, 4] and adjuvant endocrine therapy initiation and adherence [5]. While the vast majority of women with node negative, hormone receptor positive breast cancer are recommended to take endocrine therapy to reduce 10 year risk of recurrence, only about 15% of these women are thought to reap added benefit from adjuvant chemotherapy in addition to endocrine therapy [6].

In 2004, Oncotype DX (ODX) became commercially available as a tool for identifying which women with early stage, estrogen receptor positive (ER+) breast cancer are likely to benefit from adjuvant chemotherapy. ODX is a 21-tumor gene expression profiling panel that not only predicts 10-year distant recurrence, but also estimates the benefit of adjuvant chemotherapy [6]. The test categorizes women as being at “low”, “intermediate” or “high” risk of recurrence; low risk-women are predicted to derive no significant benefit from adjuvant chemotherapy, while high-risk women appear to have improved recurrence-free survival if they receive adjuvant chemotherapy in addition to endocrine therapy. Thus current guidelines recommend that women with low ODX risk scores forgo adjuvant chemotherapy and women with high risk scores receive adjuvant chemotherapy [7]. Within the intermediate group, there is less certainty regarding the benefit of adjuvant chemotherapy in terms of 10 year distant recurrence; instead adjuvant chemotherapy decision-making can be individualized for factors such as patients’ preferences, age, and comorbidities.

There are several possible ways in which the availability of ODX testing may impact racial disparities in breast cancer outcome. ODX has the potential to decrease treatment disparities -

especially among women in the low and high risk groups - because it provides an evidence-based tool to guide treatment decisions. To date, little is known about adjuvant chemotherapy decision-making in the presence of ODX risk information in a population-based study. The only peer-reviewed study to examine this question did not find racial disparities in the use of adjuvant chemotherapy among women with ODX; however findings may not be generalizable, as it was conducted within three urban, academic-affiliated hospitals [8].

Using a large, population-based prospective cohort study, we examined racial disparities in adjuvant chemotherapy initiation among women receiving ODX. To this end, we described racial differences in ODX risk scores, and we elucidated whether adjuvant chemotherapy initiation varied by race within (1) the low and high risk groups, with clear guidelines for adjuvant chemotherapy use, and (2) the intermediate group, where the treatment decision in response to ODX results is less clear. As more genetic technologies are used to manage breast cancer, it is important to understand how they impact treatment decision-making across racial subgroups.

Methods

Data Source

We used data from the third phase of the Carolina Breast Cancer Study (CBCS-III) (NIH 8389741), CBCS-III is a prospective cohort study of 2998 women with invasive breast cancer across 44 of the 100 counties in North Carolina. In collaboration with the North Carolina Cancer registry, women were enrolled using rapid case ascertainment. Notably, CBCS-III oversamples young (<50 years old) and Black women, making it ideally-suited for examining racial differences in breast cancer care. Between 2008 and 2013, patients were randomly sampled from four strata: Black women under 50 years old, Black women 50 years or older, non-Black women under 50 years old, and non-Black women 50 years or older [9]. For this study, we used data that were collected from the baseline surveys, medical record abstractions, and pathology reports to define demographic and socioeconomic, treatment, and tumor characteristic variables, respectively.

Sample

Included women met the following criteria: a single breast tumor (n=2943), ER+ (n=2139), stage I-II (n=1786), HER2 negative breast cancer (n=1507), and ODX test results (n=578). Exclusion

criteria included: undetermined tumor grade (n=4), missing data (tumor size and/or PR status) (n=6), unreported employment (n=4) and family income (n=23) (Appendix 5). Our total sample size for this study was 541 women (Black=186, non-Black=355).

Measures

Dependent variable: Our primary outcome was adjuvant chemotherapy initiation, defined as chemotherapy initiation following the primary surgery as determined from medical records.

Independent variable**:** Race was self-reported, and dichotomized in the CBCS-III as "non-African American" (non-Black) (including 93.5% White, 2.3% Asian, and 4.2% other) or "African American" (Black), irrespective of Hispanic ethnicity.

Covariates**:** Covariates included clinical (comorbidities, age at diagnosis), tumor (size, grade, ODX risk score, node status), treatment (lumpectomy vs. mastectomy), and socioeconomic characteristics. Age at diagnosis was dichotomized (< 50 versus $\geq$50 years old). We calculated the number of comorbidities recorded in patient medical records. We considered five comorbidities that are clinically likely to affect adjuvant chemotherapy decision-making: heart disease, hypertension, obesity, diabetes, and chronic obstructive pulmonary disease. Tumor and treatment characteristics were abstracted from the pathology report and medical reports, respectively. Socioeconomic variables included: marital status (married/living as married vs. other), education (less than high school, high school, or college and more), current employment since diagnosis (yes, no), family income (<15K, 15-30K, 30-50K, >50K per year), and insurance type (insured, uninsured).

Analyses

To account for complex survey design using population weights, descriptive analyses used weighted linear regression for continuous variables and weighted chi-square tests for binary/categorical variables. We compared the distribution of ODX risk scores in the sample overall and by race. We also graphed the kernel density of ODX risk scores by race. We compared sample characteristics by race and by adjuvant chemotherapy initiation. Per our data-use agreement, data were not reported for cell sizes less than or equal to 5 observations. For our primary analysis, we employed a modified Poisson regression to examine the association between race and adjuvant chemotherapy initiation. Modified Poisson regression estimates relative risk consistently and

efficiently with correlated binary outcomes, using sandwich standard errors [10, 11]. We addressed complex survey design through sample weights and design effects using Taylor Series Approximations. We also accounted for clustered standard errors at the provider level, and we conducted a complete case analysis (missing data, n=37).

We used the Institute of Medicine (IOM) definition of health disparity to guide covariate inclusion. Specifically, the IOM model for disparities states "the difference in treatment or access not justified by the differences in health status or preferences of the groups;" implying that race is a social construct [12] [13]. Thus, we did not include socioeconomic variables (marital status, education, current employment, family income, and insurance type) in our primary model, which measured the reduced form effect of race on adjuvant chemotherapy use. In order to observe the residual direct effect of race on adjuvant chemotherapy use, we also estimated a secondary model including socioeconomic covariates. This secondary model may provide insight into any mediating effects of socioeconomic factors on racial disparities.

A priori, we specified that we would stratify analyses by ODX risk category: low (risk score <18), intermediate (risk score 18-30), and high (risk score >30), because the evidence-based guidelines for adjuvant chemotherapy differed across ODX risk groups. Because so few women in the sample were categorized with high ODX scores, we lacked sufficient power to examine multivariate relationships between race and adjuvant chemotherapy initiation. Thus, we present racial differences in this group using only an unadjusted model. Finally, we present six models including unadjusted, primary, and secondary models within low and intermediate risk group strata. Analyses were conducted using STATA software (StataCorps, College Station, TX).

Results

Racial Differences in ODX Risk Score

Overall in our sample (n=541), 54.2% of women were in the low-risk group; 37.5% were in the intermediate-risk group, and 8.3% were in the high-risk group (Table 7). There were no racial differences in the proportion of non-Black compared to Black women in the low, intermediate, and high ODX risk groups (Table 8). Within ODX risk groups, mean ODX risk scores were similar among non-Black and Black women in the high (41.6 vs. 39.6, p=0.85) and low risk groups (11.2 vs. 11.3,

p=0.42): however, Black women had a somewhat higher mean risk score within the intermediate ODX risk group compared to non-Black women (23.5 vs. 22.3, p=0.04) (Table 7, Figure 7).

Within the low and high risk groups, tumor characteristics by race were similar; except in the low risk group where Black women were more likely to have higher tumor grade than non-Black women (Table 7). In the intermediate risk group, Black women had higher ODX scores and were more likely to have progesterone receptor negative breast cancer compared to non-Black women. Treatment characteristics were similar between Black and non-Black women within all three risk groups. Comorbidities, especially diabetes and hypertension were higher in Black compared to non-Black women across risk groups. Age at diagnosis was similar across racial groups in all three risk categories; however Black women were slightly younger at diagnosis compared to non-Black in the low risk group. Socioeconomic characteristics were lower among Black women compared to non-Black women regardless of ODX risk group (Table 7).

In bivariate analyses, women who initiated chemotherapy had higher ODX risk scores, larger tumors, higher tumor grade, younger at diagnosis, less heart disease and COPD, and less likely to have Medicare (Table 8). Among those with low-risk ODX scores, only 6.1% received adjuvant chemotherapy. Conversely, among women with high-risk scores, 80.1% initiated chemotherapy, given evidence-based recommendations to do so. In the intermediate risk group, about half of patients (45.7%) started chemotherapy (Table 8).

Table 7. Patient Characteristics by Race and ODX Risk Group, Carolina Breast Cancer Study, Phase 3

		Low ODX Risk Group (54.2%) Mean (Standard Deviation) or %			Intermediate ODX Risk Group (37.5%) Mean (Standard Deviation) or %			High ODX Risk Group (8.3%)) Mean (Standard Deviation) or %		
		Non-Black	Black	p	Non-Black	Black	p	Non-Black	Black	p
	n (weighted proportion)	**195 (54.8%)**	**93 (49.8%)**	†	**131 (37.4%)**	**69 (37.9%)**	†	**29 (7.7%)**	**24 (12.3%)**	†
Tumor Characteristics	**Oncotype Dx Recurrence Score**	11.2 (3.9)	11.3 (6.6)	0.85	22.3 (3.2)	23.5 (5.9)	0.04	41.6 (7.2)	39.6 (13.1)	0.42
	AJCC Stage 1 (v. 2)	68.3	66.5	0.79	62.5	67.8	0.47	77.9	51.6	0.08
	Tumor size category			0.64			0.60			0.16
	<2cm	75.3	72.3		70.8	74.1		77.9	57	
	2+ cm	24.7	27.7		29.2	25.9		22.1	43	
	Combined grade			0.03			0.39			0.29
	1	42.3	26.3		23.1	32.2		*	*	
	2	53.2	65.2		57.8	54.2		*	25.8	
	3	4.5	8.5		19.1	13.6		79.9	68.8	
	PR Positive	96.7	97.3	0.79	89.9	72.7	0.003	67.8	55.9	0.44
Treatment Characteristics	**Chemo Initiation**	5.9	7.2	0.69	46.2	42.7	0.66	76.5	94.6	0.11
	ET Initiation	92.4	93.1	0.84	97	94.4	0.41	92.6	84.9	0.42
	Radiation Initiation	67.4	70.2	0.68	66.9	70.6	0.62	57	59.1	0.89
	Lumpectomy (v.Mastectomy)	66.3	66.5	0.98	63.5	71.7	0.27	57	62.4	0.74
Clinical Characteristics	**Age at diagnosis**	57.4 (8.7)	54.4 (15.6)	0.002	56.4 (8.7)	55.8 (15.7)	0.66	57.7 (9.8)	55.4 (17.3)	0.22

	# Comorbidities	0.7 (0.8)	1.1 (1.5)	<0.001	0.5 (0.6)	1.0 (1.4)	<0.001	0.7 (1.0)	1.4 (1.2)	0.02
	Diabetes	7.4	20.7	0.003	7.7	20.3	0.01	*	40.9	0.01
	COPD	*	*	0.62	*	*	0.56	*	*	0.59
	Obesity	14	21.3	0.13	8.7	18.2	0.1	*	31.2	0.07
	Heart Disease	4.8	*	0.19	*	*	0.3	*	*	>0.99
	Hypertension	39.8	64.9	<0.001	31.1	59.4	<0.001	43.6	66.7	0.08

*Data not reported for cell sizes of 5 or fewer. †p-value for weighted chi-square=0.23. Because of small cell size, we combined women who were diagnosed in 2013 (n=8) with women who were diagnosed in 2012, and women who had tumor size >5cm (n=5) with women who had a tumor size of 2-5 cm

Table 8. Sample Characteristics by Adjuvant Chemotherapy Initiation, Carolina Breast Cancer Study, Phase 3.

		Overall Sample Mean (Standard Deviation) or %		
		No Chemotherapy	Chemotherapy	p
	n	373	168	
Tumor Characteristics	Oncotype Dx Recurrence Score	14.4 (6.6)	27.6 (11.4)	<0.001
	ODX Risk Group			
	Low	93.9	6.1	<0.001
	Intermediate	54.3	45.7	
	High	19.9	80.1	
	< 2cm Tumor size (vs. 2cm+)	76.9	64.2	0.01
	Combined grade			<0.001
	1	36.8	18.3	
	2	55.2	44	
	3	8	37.7	
	PR Positive	92.3	86.4	0.06
Treatment Characteristics	ET Initiation	93.1	96.1	0.25
	Radiation Initiation	68.4	62.4	0.24
	Lumpectomy (v. Mastectomy)	65	68	0.03
Clinical Characteristics	Age at diagnosis	58.0 (9.4)	53.6 (11.3)	<0.001
	# Comorbidities	0.7 (0.9)	0.6 (0.9)	0.4
	Diabetes	9.4	10.3	0.78
	COPD	2.5	*	0.12
	Obesity	12.7	13.2	0.87
	Heart Disease	4.5	*	0.001
	Hypertension	40.9	38.9	0.7
Socioeconomic Characteristics	Annual Family Income			0.98
	<15K	7.6	7.2	
	15-30K	13.3	13	
	30-50K	18.8	17.4	
	>50K	60.4	62.4	
	Insurance			
	Private	79.2	82	0.55
	Medicaid	6.2	8.5	0.41
	Medicare	35.2	23.9	0.05
	Uninsured	2.6	4	0.41
	Married	69.8	70.7	0.85
	Employed (v. Unemployed)	49.7	51.3	0.78

	Education			0.93
	HS & Post-HS	48.5	48.3	
	College+	46.5	45.7	
	<HS	5.1	6	
Year of Diagnosis	**Year**			0.07
	2008	8.5	18.1	
	2009	19.8	17.1	
	2010	25.4	20.7	
	2011	23.4	26.8	
	2012/2013	23	17.2	

*Data not reported for cell sizes of 5 or fewer. Because of small cell size, we combined women who were diagnosed in 2013 (n=8) with women who were diagnosed in 2012, and women who had tumor size >5cm (n=5) with women who had a tumor size of 2-5cm

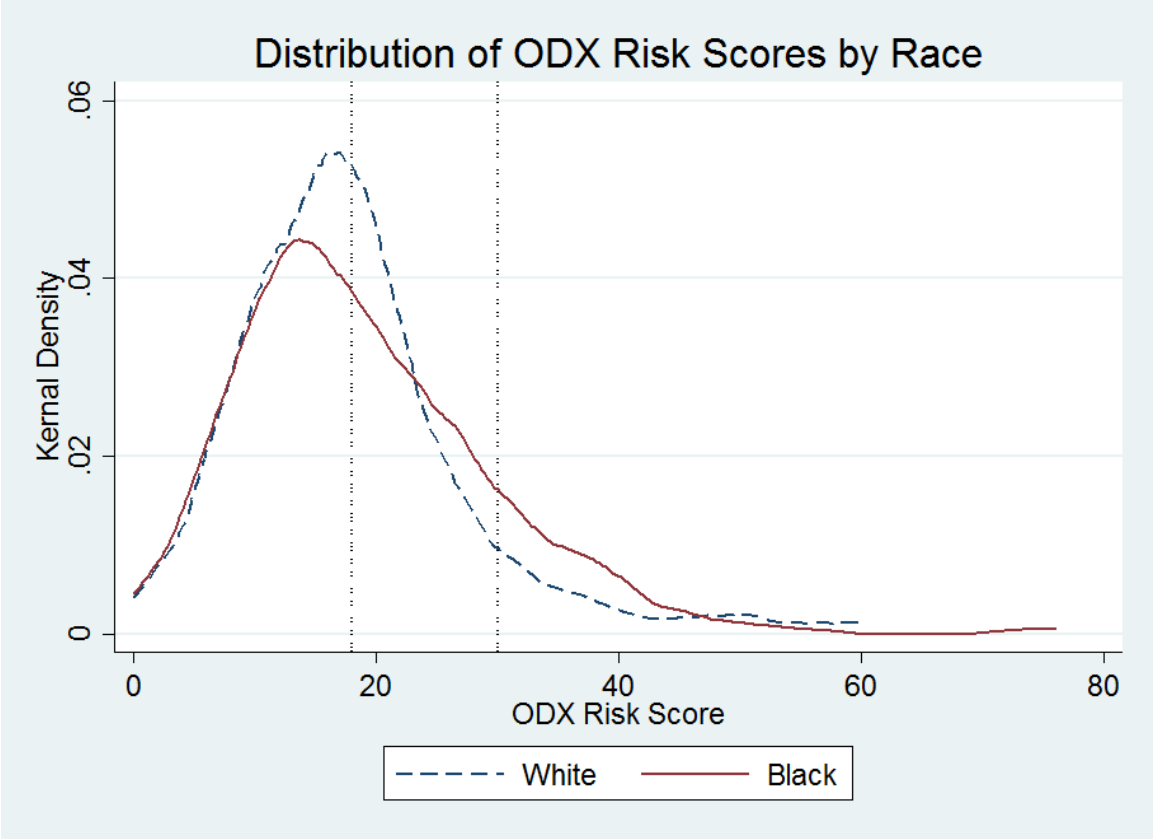

Figure 7. Distribution of ODX risk scores by race, with reference lines indicating cut off points (at 18 and 30 scores) for the low-, intermediate-, and high- risk groups[6].

Racial Differences in Adjuvant Chemotherapy Initiation in Risk Groups: Higher Treatment Certainty in Guidelines

Low Risk Group: No association between race and adjuvant chemotherapy uptake was observed within the low risk group (Table 9). Higher ODX scores among those in the low risk category were associated with an increased likelihood of chemotherapy initiation compared to other women within this subgroup, holding other factors constant in both the primary and secondary models (primary aRR 1.35, 95%CI=1.17-1.55, p<0.001; secondary aRR 1.39, 95%CI=1.22-1.58, p<0.001). In the secondary model, being married was also independently associated with an increased likelihood of adjuvant chemotherapy uptake in the low risk group (secondary aRR 2.92, 95%CI=1.12-7.60, p<0.028). Finally, having high versus low grade tumors (secondary aRR 3.57, 95%CI=1.08-11.76, p=0.037) and having larger tumor size (secondary aRR 3.45, 95%CI=1.28-9.29, p=0.014) were each independently associated with an increased likelihood of adjuvant chemotherapy initiation in the secondary model, but not the primary model.

High Risk Group: No racial differences were found in the initiation of adjuvant chemotherapy among women in the high risk group, though a non-significant increased risk of chemotherapy was found among AA women (unadjusted RR=1.24, 95% CI=0.94-1.62, p=0.12). The small sample size precluded our ability to explore beyond the unadjusted model.

Racial Differences in Adjuvant Chemotherapy Initiation in the Intermediate Risk Group: Lower Treatment Certainty in Guidelines

No racial differences in adjuvant chemotherapy initiation were observed; however higher ODX score (primary aRR=1.15, 95%CI=1.11-1.19, p<0.001; secondary aRR=1.15, 95%CI=1.11-1.20, p<0.001), younger age (primary aRR=2.00, 95%CI=1.39-2.89, p<0.001; secondary aRR=1.95, 95%CI=1.35-2.81, p<0.001), and tumor size ≥ 2cm (primary aRR=1.51, 95%CI=1.12-2.035, p=0.007; secondary aRR=1.70, 95%CI=1.22-2.35, p=0.002) were each independently associated with an increased risk of chemotherapy initiation across primary and secondary models (Table 10). Finally, being diagnosed in year 2012 or 2013 was associated with lower risk of adjuvant chemotherapy initiation (primary aRR=0.56, 95%CI=0.33-0.97, p<0.037; secondary aRR=0.54, 95%CI=0.30-0.96, p=0.036). In the secondary model, the lowest income patients were independently more likely to initiate chemotherapy compared to patients with higher incomes.

Table 9. Unadjusted and Adjusted Risk Ratios for the Association between Race and Adjuvant Chemotherapy Initiation in the Low ODX Risk Groups.

	LOW ODX RISK GROUP (N=285)								
	Unadjusted			Primary Model			Secondary Model		
	cRR	95% CI	P>|t|	aRR	95% CI	P>|t|	aRR	95% CI	P>|t|
Black (v. Non-Black)	**1.21**	**0.47-3.08**	**0.69**	**1.26**	**0.50-3.21**	**0.63**	**1.37**	**0.60-3.12**	**0.29**
ODX risk score				1.35	1.17-1.55	<0.001	1.39	1.22-1.58	<0.001
Node Positive (v. negative)				0.81	0.28-2.29	0.68	0.77	0.20-2.96	0.70
< 50 Years Age at Diagnosis				2.32	0.79-6.80	0.12	2.12	0.66-6.85	0.21
2+ cm Tumor size (v. <2cm)				2.53	0.99-6.43	0.052	3.45	1.28-9.29	0.014
Grade (v.1)									
2				0.82	0.34-2.00	0.66	0.87	0.32-2.35	0.78
3				1.88	0.52-6.83	0.33	3.57	1.08-11.76	0.037
Mastectomy (v. Lumpectomy)				1.65	0.70-3.92	0.25	1.61	0.69-3.76	0.27
# of Comorbidities				1.3	0.76-2.24	0.34	1.3	0.73-2.33	0.37
Family Income (v. <15K)									
15-30K							1.29	0.29-5.69	0.736
30-50K							1.14	0.24-5.39	0.87
>50K							0.58	0.11-3.17	0.53

Uninsured (v. insured)							0.8	0.17-3.64	0.77
Married (v. unmarried)							2.92	1.12-7.60	0.028
Employed (v. unemployed)							0.68	0.20-2.26	0.53
Education (v. HS-HS+)									
College+							2.86	0.92-8.9	0.07
<HS							0.7	0.059-8.32	0.78
Year									
2009				0.71	0.14-3.47	0.67	0.77	0.15-4.01	0.76
2010				1.7	0.41-7.17	0.47	1.78	0.36-8.81	0.481
2011				0.57	0.12-2.68	0.48	0.36	0.069-1.87	0.22
2012/2013				0.38	0.060-2.41	0.30	0.34	0.044-2.58	0.29
Constant	0.059	0.034-0.10	<0.001	<0.001	<0.001-0.005	<0.001	<0.001	<0.001-0.002	<0.001
Population N									1008
#PSUs									190
Design df									186

PSU= Primary Sampling Unit is the provider to account for provider level variation. Because of small cell size, we combined women who were diagnosed in 2013 (n=8) with women who were diagnosed in 2012, and women who had tumor size >5cm (n=5) with women who had a tumor size of 2-5cm

Table 10. Unadjusted Risk Ratio for the Association between Race and Adjuvant Chemotherapy Initiation in the Intermediate ODX Risk Group

	INTERMEDIATE ODX RISK GROUP (N=199)								
	Unadjusted			Primary Model			Secondary Model		
	cRR	95% CI	P>|t|	aRR	95% CI	P>|t|	aRR	95% CI	P>|t|
Black (v. Non-Black)	0.92	0.64-1.33	0.67	0.88	0.64-1.22	0.45	0.92	0.62-1.36	0.67
ODX risk score				1.15	1.11-1.19	<0.001	1.15	1.11-1.20	<0.001
Node Positive (v. negative)				1.22	0.82-1.82	0.31	1.12	0.76-1.64	0.56
< 50 Years Age at Diagnosis				2.00	1.39-2.89	<0.001	1.95	1.35-2.81	<0.001
2+ cm Tumor size (v. <2cm)				1.51	1.12-2.035	0.007	1.70	1.22-2.35	0.002
Grade (v.1)									
2				0.88	0.60-1.30	0.53	0.88	0.60-1.27	0.49
3				1.086	0.72-1.63	0.69	1.16	0.77-1.75	0.49
Mastectomy (v. Lumpectomy)				0.89	0.64-1.23	0.48	0.84	0.61-1.17	0.30
# of Comorbidities				0.87	0.67-1.13	0.29	0.85	0.65-1.12	0.24
Family Income (v. <15K)									
15-30K							0.30	0.12-0.77	0.013
30-50K							0.33	0.15-0.75	0.009
>50K							0.43	0.18-1.012	0.053
Uninsured (v. insured)							1.23	0.58-2.63	0.59
Married (v. unmarried)							1.22	0.78-1.93	0.38
Employed (v. unemployed)							1.31	0.94-1.83	0.108
Education (v. HS- HS+)									
College+							0.84	0.59-1.18	0.31
<HS							0.74	0.26-2.13	0.57
Year									
2009				0.85	0.48-1.51	0.58	0.91	0.49-1.68	0.76
2010				0.72	0.36-1.45	0.35	0.76	0.36-1.58	0.45
2011				0.99	0.61-1.62	0.98	1.013	0.61-1.70	0.96
2012+				0.56	0.33-0.97	0.037	0.54	0.30-0.96	0.036
Constant	0.46	0.39-0.55	<0.001	0.019	0.0054-0.068	<0.001	0.031	0.0086-0.11	<0.001
Population N									698
#PSUs									145
Design df									141

PSU= Primary Sampling Unit is the provider to account for provider level variation. Because of small cell size, we combined women who were diagnosed in 2013 (n=8) with women who were diagnosed in 2012, and women who had tumor size >5cm (n=5) with women who had a tumor size of 2-5cm.

Discussion

Overall, we found no racial disparities in adjuvant chemotherapy initiation across ODX risk groups; neither did we observe racial differences in mean ODX risk scores within the high and low risk groups. However, in the intermediate risk group, Black women had slightly higher ODX risk scores compared to non-Black women. The magnitude of this difference was small, and likely not clinically meaningful, corroborating a previous study that reported no significant racial differences in mean ODX risk scores [8]. Unlike that study, we did not observe significant racial differences in the distribution of women into ODX risk groups [8].

In our study, only 8% of women were classified with high risk scores. This differs significantly from the preliminary ODX validation studies, where 27% of women with early stage breast cancer were classified as high risk [6]. Notably, subsequent observational studies have found the proportion of high-risk scores to be similar to what we observed [8]. In a qualitative study, providers discussed being less likely to order ODX testing for more aggressive tumors because they felt that they already had the necessary information to offer adjuvant chemotherapy [14]. Thus, this may suggest reasons why women with high risk scores may be less likely to receive ODX testing in real world practices.

We did not find racial disparities in adjuvant chemotherapy initiation. There are several plausible explanations for this finding. First, we examined women with early stage, ER+, HER2- breast cancer who received ODX testing. Within this selected group, it is possible that women already have access to high quality breast cancer care that would attenuate racial differences in uptake of chemotherapy. Second, it is possible that ODX information mediates variation in the uptake of adjuvant chemotherapy by providing an objective tool to guide treatment decision-making. Third, the non-significant association between race and adjuvant chemotherapy initiation may result from our relatively small sample size, especially in multivariate models. Finally, studies of racial variation in breast cancer care have not consistently demonstrated racial disparities in adjuvant chemotherapy initiation. While some studies report underuse of adjuvant chemotherapy among minority and low-income women [3, 4, 15], others have failed to find such disparities [16-18]. Furthermore, some studies suggest that racial disparities in adjuvant chemotherapy use occur not in initiation, but rather in delays [19-21], which was not evaluated in our study.

Although race was not associated with adjuvant chemotherapy initiation across risk groups, there were interesting findings within the low and intermediate risk groups. Despite guideline recommendations to forgo chemotherapy for low ODX risk tumors, a small subgroup of patients (6.1%) still initiated adjuvant chemotherapy. Within the low risk group several factors were independently associated with adjuvant chemotherapy initiation. Higher ODX score was associated with an increased likelihood of chemotherapy initiation. This may reflect that ODX scores are being used along a continuum; if so, within risk groups, physicians may perceive some women to be at higher risk than others. In our secondary model, other tumor characteristics, including larger tumor size (>2cm v. <2cm) and higher tumor grade (3 vs. 1), were each independently associated with increased risk of chemotherapy initiation, suggesting that such tumor characteristics play a role in adjuvant chemotherapy initiation even in the presence of a low ODX risk score. Finally, consistent with previous literature, being married was associated with an increased likelihood of adjuvant chemotherapy initiation among women in the low-risk group. It may be that women who are married have more social support and resources to pursue additional treatments [22].

Interestingly, population weighted estimates demonstrated that 19.9% of patients in the high risk group failed to initiate adjuvant chemotherapy despite guidelines. Small sample size limited our ability to investigate factors associated with adjuvant chemotherapy receipt in this group. Qualitative analyses suggest that women who forgo chemotherapy in this group typically do so because of patient preferences [14].

Within the intermediate group, about half of women received chemotherapy. Race did not influence chemotherapy initiation: however, similar to the low risk group, the ODX risk score did. Not only higher ODX score, but also larger tumor size was associated with adjuvant chemotherapy initiation. Taken together, tumor characteristics appeared to play a major role in directing adjuvant chemotherapy decision-making within the intermediate risk group. Younger age was also associated with higher risk of adjuvant chemotherapy initiation in the intermediate group, which is consistent with studies demonstrating that younger women tend to get more aggressive treatment [14, 23]. This could be due in part to better overall health and tolerability of adjuvant treatment, patient preferences, or other differences in tumor characteristics. Interestingly, having an annual family income below

$15,000 was associated with a higher likelihood of adjuvant chemotherapy initiation compared to women with higher incomes. Two potential explanations for this finding may be that (1) low income patients are more likely to be seen by providers that prescribe more chemotherapy within the intermediate risk group or (2) patient preferences regarding chemotherapy vary by socioeconomic factors, such as family income. Finally, being diagnosed with breast cancer in 2012 or 2013 was associated with a lower likelihood of adjuvant chemotherapy use, perhaps indicating a change in practice patterns over time.

This study has several limitations. First, while CBCS-III is a large, longitudinal breast cancer cohort that oversamples Black women, we were underpowered to fully explore racial disparities in multivariable models, particularly in the high risk group. Second, we were unable to account for patient preferences, which likely play a role in ordering ODX testing and subsequent adjuvant chemotherapy decision-making [24]. Third, we lacked data on organizational and provider characteristics that influence adjuvant chemotherapy use [8, 25, 26]. Finally, we conducted a complete case analysis under the assumption that data were missing at random. If this assumption is violated, then estimates may be biased. However, we did not observe significant differences in race, ODX risk score or chemotherapy initiation between observations with missing and non-missing data field(s).

Our study adds to the literature by investigating the uptake of adjuvant chemotherapy among women receiving ODX testing by race within a large longitudinal, population-based cohort study of breast cancer patients. Our findings suggest that racial disparities in adjuvant chemotherapy use do not exist among this group of breast cancer patients receiving ODX. As more genetic technologies are incorporated into treatment decision-making, it will be important to understand how these tests are being used across racial subgroups. Future research should incorporate organizational-, provider-, and patient- level data into studies that seek to understand racial variation in oncology treatment decision-making.

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CHAPTER 6. BARRIERS AND FACILITATORS FOR ONCOTYPE DX USE AMONG ONCOLOGISTS: A QUALITATIVE STUDY

Background

Once viewed a single disease, breast cancer is now recognized as a heterogeneous disease with distinct biological subtypes (1). With this nuanced recognition of tumor biology, we better understand the interaction between tumor genetics and treatment response. As such, genetic technologies are changing the landscape for breast cancer treatment.

Oncotype DX (ODX) is a 21-tumor gene-profiling panel test that estimates 10-year risk of recurrence and benefit of adjuvant chemotherapy among early-stage, estrogen receptor positive (ER+) breast cancer patients, thereby improving treatment decision-making (2). Specifically, women with low risk scores are recommended to forgo, and women with high risk scores to take, adjuvant chemotherapy; research on chemotherapy benefit among women with intermediate risk scores is ongoing (3). Evidence suggests that ODX reduces adjuvant chemotherapy use among women with low risk scores, saving patients from significant costs and harms of adjuvant chemotherapy overuse (4-6).

Today, ODX use has been incorporated into standard practice. Some private insurers began reimbursing for ODX in 2005, and CMS followed in 2006 (7). Although clinical guidelines began recommending ODX in 2007 (7), fewer than half of guideline-eligible women are receiving ODX testing (8-11). Reasons for its low use are not well understood. Because treatment decision-making is a nuanced process, secondary data are unlikely to capture the complex factors related to ODX use and subsequent adjuvant chemotherapy decision-making. Thus, this study sought to better understand provider recommendation patterns for ODX, and to identify factors that influence ODX test use at the organizational, interpersonal, and intrapersonal levels.

Methods

Study Design

We conducted semi-structured telephone interviews with oncologists across North Carolina (NC) The interview guide was motivated by a conceptual model (12) in which barriers and facilitators influencing providers' use of ODX could occur at the organizational, interpersonal, and intrapersonal levels. We conducted interviews until theme saturation was reached (estimated ~15-20). Interviews took ~30 minutes and were conducted by one author (MCR); a second author (AB) listened, identified areas for probing, and took notes. All interviews were digitally recorded, professionally transcribed, de-identified and transferred to Atlas.ti (Berlin, Germany) for analysis.

Table 11. Participant Characteristics.

Characteristics		Mean
Provider	Gender (%Male)	53.3
	Race (% White vs. Non-white)	86.7
	Oncology Specialty (% Medical vs. Surgical)	66.7
	Years of practice	15.8 $\pm$ 7.8
	Number of ODX ordered per month	4.4 $\pm$ 3.4
Patient Mix	Medicaid (%)	20.7
	Uninsured (%)	10.5
	Non-White (%)	38.1
	Breast Cancer Patients (%)	56.4
	Breast Cancer Patients/wk (%)	25.1 $\pm$13.9
	Breast Cancer patients with HR+ breast cancer (%)	68.1
Practice	Academic Affiliation (%)	73.3

Procedures

We used purposive sampling to identify NC surgical and medical oncologists who practice in community or academic settings through the: (1) NC Oncology Association and NC Medical

Licensure websites and (2) contacts with clinical partners. Providers were emailed or faxed a recruitment letter, asking those interested in participating to contact the researchers. Providers were eligible if they saw ≥5 breast cancer patients/week to establish care, undergo treatment, or for follow-up. Once we scheduled a phone interview, providers completed an electronic informed consent and brief demographic survey. We gave providers $100 gift cards for their participation.

Data Analysis

We used template analysis which combines inductive and deductive approaches to qualitative analysis by allowing *a priori* codes to be modified, removed and augmented (13). Template analysis follows several steps. First, our initial coding template applied the domains of the conceptual model (12), including "attitudes towards the innovation", "organizational facilitators/internal marketing," "social usage" and "personal dispositional innovativeness" as *a priori* codes. We applied the initial coding template to the first five interview transcripts using Atlas.ti. Subsequently, the initial template was revised and emergent thematic codes were added in a hierarchical fashion to create a final coding template (Appendix 6) that was applied to all transcripts: MCR and AB coded all transcripts. Consensus was reached on coding for the first five transcripts to ensure agreement across coders; coders' analytic files were merged using Atlas.ti. Data were analyzed and organized by: provider recommendation patterns, as well as factors that influenced ODX use at the organizational, interpersonal, and intrapersonal levels.

Results

Provider Characteristics

After interviewing 5 surgical and 10 medical oncologists across 10 health care settings, theme saturation was reached (Appendix 7). Provider characteristics are presented in Table 11. On average, participants ordered ~4 ODX tests/month and had practiced for about 16 years. They saw an average of 25.1 breast cancer patients/week and estimated that ~70% of their patients had hormone receptor positive breast cancer. When asked "among my peers, I am usually the first to try out new medical technologies for clinical care" on a Likert scale (1=strongly agree; 7=strongly disagree), their mean score was 3.3 (viewing themselves as somewhat innovative).

ODX Recommendation Patterns

Factors influencing provider recommendation for ODX testing crosscut organizational, interpersonal, and intrapersonal levels. Providers typically determined eligibility for ODX based on tumor characteristics, age, comorbidities, and patient preferences. Though variation existed, most providers felt that patients with HER2 negative, ER+, stage 1 and node negative breast cancer were appropriate candidates for ODX. While a few providers restricted their use of ODX to Stage 1 only, the majority considered Stage 2 breast cancers. Overall, this aligns with current clinical guidelines recommending ODX for HER2 negative, ER+, stages 1-2, node negative, >0.5cm tumors (14).

Providers were less likely to use ODX for women who may not be candidates for chemotherapy due to extensive comorbidities, advanced age or life expectancy <10 years. Young age seemed to influence ODX test use in two ways. First, one provider mentioned a bias towards adjuvant chemotherapy in younger women, making ODX testing unnecessary. Second, two providers mentioned a lack of validated data for ODX test use among premenopausal women, resulting in less use:

> I do acknowledge that even though the original publication of the Oncotype validation tried to say that age really wasn't a factor...I'm still not totally convinced of that. I think that there is some reason to doubt that it functions in quite the same way in younger women. Those patients oftentimes will decide to take chemotherapy anyway; not often but a handful.

While many providers felt that most patients are open to receiving ODX, patient preferences played a large role. The vast majority of providers reported being unlikely to order ODX if a patient expressed a clear preference against chemotherapy because the test result would not provide actionable information. Several providers stated that prior to ordering ODX, they discussed patient preferences so patients understood how the ODX risk score might inform their decision about adjuvant chemotherapy. When a patient's preference towards chemotherapy was not aligned with how the ODX score could influence treatment decisions, providers often did not order ODX.

The most variation in ODX testing was in node positive disease: Currently, ODX testing in node positive disease is not guideline recommended; however, new evidence suggests it may be applicable [14]. Twelve providers mentioned ordering ODX for node positive patients less frequently than in node negative patients. Many providers referenced only using ODX for node positive patients

in two major ways. First, providers used patient enrollment into the RxPONDER study (15) to motivate the use of ODX among certain women with positive lymph nodes. While women with 1-3 positive lymph nodes were eligible for the RxPONDER study, some providers only ordered ODX for women with 1-2 positive nodes. Most providers were comfortable recommending ODX among patients with otherwise favorable histological (e.g., lobular) and tumor (e.g., low grade, small size) characteristics. Second, providers commonly reported ordering ODX in node positive disease to find evidence to forgo chemotherapy in elderly, sick, or frail patients. Many providers expressed no hesitation in using ODX among women with micro-metastases. Hesitation around using ODX testing in node positive patients largely came from lack of evidence that ODX predicts chemotherapy benefit in this population.

Organizational-Level Factors

One organizational challenge to ODX testing resulted from departmental silos (surgical versus medical oncology; pathology versus oncology). Providers mentioned that departmental silos were more common when ODX was first introduced, suggesting an organizational learning curve:

> I think how it was working before is we would call the pathology department…my nurse would have to walk up there, get the blocks herself, get the Oncotype kit, fill out all the paperwork, and mail it. Now we just call pathology and they mail it. They kind of leave that whole step out.

Several providers indicated that having a single nurse or staff member responsible for ordering ODX might address this challenge. Furthermore, provider roles in ordering ODX shifted to a more organized process over time:

> At present, just the medical oncologists are [ordering the test]. When the test first came out and before we actually formulated the multidisciplinary breast group, we had radiation doctors ordering it and surgeons ordering it...And so it wasn't really being used appropriately in every instance. It was nice sometimes to have the results available right then when you talk to the patient. But that wasn't appropriate in all the situations. So [now], we basically have an understanding that it should be done by med oncologists.

Overall, multidisciplinary teams seemed to facilitate decision-making about which patients would benefit from ODX and provided an optimal organizational structure for ODX use:

> It's actually very simple [to order] because we have a multidisciplinary clinic where we have a medical oncologist and a surgeon working side by side all day long every day. So, we literally just walk over with the path report, say 'Ms. X has just come back from the operating room for a return cancer operation.' We decide what to do and move ahead.

These multidisciplinary teams appeared to reduce departmental silos as a barrier to test use.

All providers, except one who could not recall, had at least one interaction with the Genomic Health Marketing team. In general, Genomic Health representatives and/or resources seemed to facilitate ODX use through: (1) training for ordering and using ODX, (2) offering support around coverage/reimbursement for ODX, and (3) providing educational materials and current research results around its effectiveness. Providers also indicated that easy online ordering and results, website resources, and printable test reports facilitated use of ODX.

Ten providers discussed insurance coverage. In node positive patients, insurance coverage, outside of clinical trial use, was often seen as a barrier for using ODX. Providers noted that insurance policies did not "keep up with the science," referencing new studies that demonstrate effectiveness of ODX in node positive disease. Notably, insurance was no longer viewed as a barrier for women with node negative disease. This suggests that if evidence accumulates for using ODX in node positive disease, clinical guidelines and insurance coverage may change accordingly. Until then, several providers noted that Genomic Health offers payment assistance programs for eligible patients for whom insurance does not fully cover the cost of ODX.

Organizational factors identified as barriers to ODX use delayed, rather than prevented, sending results to Genomic Health. One provider noted:

> The biggest delay I've seen is from insurance companies making approval. And most end up doing it. Like I said before, very few have said "no." But that's usually the biggest delay is them dragging their feet to approve it and it adds another week or two. …this isn't as big anymore...

Another provider elaborated how these delays influence the patient:

> It's not something we typically order off of the core biopsy because we just don't have all the answers yet. […] So, once surgery is completed and you've got a pathology report then there's still a delay … and so it drags things out for the patient. And there's an anxiety associated with that.

While delays were not viewed as compromising treatment trajectory, they were inconvenient to patients and increased their anxiety. Two providers emphasized that these delays can be particularly difficult for patients living in rural areas or travelling long distances for care.

Interpersonal-Level Factors

Providers discussed physicians' normative beliefs and roles on their use of ODX. Overall, providers believed that there was greater buy-in for ODX compared to alternative tumor gene profiling panels. Several providers referenced consensus around ODX use for managing early stage, ER+ breast cancer. Because medical oncologists typically ordered ODX, discussed ODX results with patients, and ordered adjuvant chemotherapy, the ODX recommendation often came from them rather than surgical oncologists. While medical and surgical oncology roles were sometimes well-coordinated, discordant beliefs and disagreements occurred between surgical and medical oncologists who used different criteria for ODX recommendation. For example, one medical oncologist stated:

> One [surgical oncologist] doesn't order it. The other one does, and it drives me nuts because they order it for HER2 positive patients. They order it on a four-millimeter patient.... It puts me in a bind. [...] I never would have ordered it or even brought it up.

One surgical oncologist discussed introducing ODX to patients before they see their medical oncologist, because ODX is not used across the board:

> I will discuss Oncotype as part of "this may play a role in determining whether you benefit from chemotherapy." And I do that as part of my discussion as the surgeon so that it puts it out on the table and then [they] can force the issue with the medical oncologist. I work with a wide variety of medical oncologists. And while it's now more in the standard, it is not completely embraced across the board.

Some providers mentioned that ODX recommendations beyond node negative patients are becoming more common, but norms vary across health care settings:

> I traditionally order Oncotype in my node negative, ER positive patients. I know across the United States there's been more of a push to use Oncotype in the node positive.
>
> There are people who use it kind of emphatically in the one to three lymph node group. I think I use it still more sparingly until we have prospective data, which we should have soon.

Intrapersonal-level Factors

Most providers referenced attitudes and beliefs when discussing ODX use, which we grouped into three categories: attitudes towards ODX, perceived barriers, and perceived research gaps

Attitudes Toward ODX

Overall, providers had positive attitudes towards ODX, because it provided clinically relevant results that providers and patients could use to make treatment decisions, saving some patients from a major treatment from which they were unlikely to benefit:

> Quite honestly, [they] used to be frustrating discussions for all of us, because we knew that there was a significant portion of the ER positive node negative disease that we were giving chemotherapy where we probably were not benefitting patients at all.

One provider noted that test results helped frame discussions with patients regarding their future health and survival:

> It's oftentimes the case in early stage breast cancer discussion that the focus…very quickly, goes to the local, regional management. And that's fine to some degree. But it can't come at the cost of patients losing sight of the importance of the systemic therapy. Ultimately, … the discussion I think helps to put the issue and the problems they need to think about in the right context. One of the strengths is [that it] quantifies their risk in a way that for most patients is quite reassuring.

Some providers mentioned that patients are increasingly familiar with ODX when they enter their offices, facilitating patient understanding of the test and results. Providers saw several other reasons for using ODX over alternative tumor gene profiling panels. For example, ODX does not require fresh tissue (like Mammaprint), making it more convenient and feasible, especially in small, rural communities. Two providers noted that the receptor status information that ODX provides is useful to ensure that patients' tumors are properly classified.

Providers' Perceived Barriers

Providers discussed frequent difficulty with communicating the purpose of ODX testing to patients:

> I'm always talking about genetic testing and I think sometimes they can confuse Oncotype DX testing with genetic testing with BRCA 1 and 2. […] Either they're very overwhelmed or I'm not explaining it clearly enough or it's not concrete enough at that point in their process of their treatment.

Furthermore, explaining risk of recurrence and risk reduction was challenging because the nuances involved often led to "information overload." One provider reported that low risk scores can result in misconceptions about the need for other risk reduction strategies. For example, women with low ODX risk scores may interpret the result to mean that adjuvant therapy is unnecessary, when in reality

endocrine therapy is still recommended. Patient misconceptions occurred not only about the test and its interpretation, but also about its perceived cost, which can be a barrier to testing. To overcome patients' misconceptions, several providers emphasized the need to discuss ODX across multiple visits.

Overall, providers discussed that low risk patients forgo chemotherapy and high-risk patients receive chemotherapy. Discordant chemotherapy decisions were rare, and often resulted from patient preferences. However, intermediate risk results posed a challenge to providers. Providers often created rules for navigating adjuvant chemotherapy decision-making in the intermediate ODX risk group. About half of the providers created their own cut-off points within the intermediate group for recommending adjuvant chemotherapy. One provider stated that as a rule, s/he recommends adjuvant chemotherapy to most patients within the intermediate risk group; another provider rarely did so. About 1/3 of providers used "old fashioned" clinical and tumor characteristics (tumor size, grade, age, comorbidities) when recommending chemotherapy in the intermediate risk group. Because there is no definitive evidence of benefit to chemotherapy in this risk group, providers emphasized the importance of patient preferences in decision-making. Most providers used a combination of approaches for decision-making in the intermediate risk group: For example:

> It's a joint decision about whether or not to give chemotherapy […] if it's towards the low end of intermediate, I'm comfortable not giving chemotherapy. If it's towards the high end, then I'm more likely to recommend chemotherapy--but add into that also such things as age.

Perceived Research Gaps

Providers offered ideas about future research needs including (1) what patients understand about ODX and (2) how to best communicate ODX testing and results with patients. Providers also reported a need to better understand the predictive validity of ODX among premenopausal women, pointing to weaknesses in current studies that underrepresent younger women. Because women in validation studies were taking endocrine therapy, one provider discussed the need to understand ODX's predictive validity when patients are not prescribed or appropriately taking this therapy. They also wanted more studies of ODX effectiveness in real world settings and that consider additional patient outcomes (e.g., survival). Several providers desired more information about managing women with intermediate risk scores and hope that the TAILORx trial will soon close this research gap (3).

Finally, oncologists voiced a need for genetic technologies that not only describe which patients would benefit from chemotherapy, but also *which* chemotherapy regime would be most effective.

Discussion

Our findings contributes to current knowledge by providing a rigorous, theory-driven, qualitative study examining how multilevel factors influence ODX recommendation and use among providers. We elicited how organizational, interpersonal and intrapersonal factors have influenced ODX use and explored nuances across node positive and node negative breast cancer patients.

Prior research indicates that the diffusion of genomic innovations is influenced by multilevel factors (16). Currently only two qualitative studies have examined provider and system-level factors that influence the use of ODX in clinical care, one of which focused more broadly on barriers common to both BRCA and ODX testing (17). Together, these studies indicated that characteristics of the test (i.e., interpreting intermediate results)(18), use of multidisciplinary teams (18), test coordination (including reimbursement) (17), and patients' out-of-pocket costs (17) created barriers to genetic technologies in clinical practice. Furthermore, oncologists worried that testing could be used inappropriately(18) or delay treatment (17). Overall, our study found similar results; however, most providers in our study viewed multidisciplinary teams as facilitators to ODX use. Previous studies also indicated that costs were a barrier for ODX use. While we found this to be true for node positive patients, costs were rarely reported as a barrier for node negative patients. Furthermore, it is possible that stage of adoption and insurance coverage of ODX varied across study settings (19).

Organizational factors, including departmental structure, workflows for ordering tests and insurance policies, were discussed frequently by providers in our study. The extent to which these factors acted as barriers seemed to decrease over time, suggesting that organizational barriers may be especially critical to address when first adopting of genetic technologies. Furthermore, providers' normative beliefs have changed over time to embrace ODX in the node negative setting; with increasing evidence, beliefs are beginning to shift in node positive disease.

Research evidence was viewed as essential to provider acceptance of ODX. Respondents sought evidence from research among real world patients; cancer registries and health information technology will be critical to evaluating these technologies. Because patients demonstrate poor

understanding of ODX and its interpretation results (20, 21), future research should examine best practices for how providers communicate this information so that they can optimally use results from genetic tests to help patients make informed treatment decisions. Equally important, guideline support and insurance coverage for these technologies will be important in facilitating their use. Rapidly incorporating these technologies into insurance policies and practices may present challenges for policy makers. It will be imperative that financial barriers do not preclude low socioeconomic patient subgroups from accessing these technologies and contribute to existing disparities in access and quality care.

The main limitation of this study is generalizability: (1) we only included NC providers, (2) respondents may differ from providers who declined to participate, and (3) while saturation of themes was attained, the sample consists of 15 provider perspectives.

ODX represents an example of the successful genetic technology that has reshaped breast cancer care for women with early stage breast cancer. As such, it presents an important model for incorporating a genetic technology into the standard of cancer care. Our findings highlight the importance of multi-level factors in the use of ODX testing. Moving forward, studies should examine how the identified organizational factors influence uptake and use of ODX, controlling for provider-level variation. As more genetic technologies become available, our findings can facilitate their uptake across providers and health care settings. Finally, more evidence is needed to truly understand the effectiveness of ODX in treatment decision-making and outcomes (22).

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CHAPTER 7. DISCUSSION

Conclusions

Race and ODX Use

Findings from this study provide insight into how the ODX test is being incorporated into cancer care. While racial disparities were not detected among women with node negative breast cancer, a racial difference was detected among node positive patients: Black women with positive lymph nodes had a 46% decreased chance of receiving ODX testing compared to non-Black women. We offer several hypotheses as to why ODX may be used differently among node negative verses node positive patients.

First, ODX is widely covered for adjuvant chemotherapy decision-making in node negative patients and has been incorporated into clinical guidelines; neither is true for node positive patients. Thus, the lack of insurance coverage for ODX testing in node positive may play a role in the observed difference in testing. Notably, when SES factors such as education, family income, and insurance coverage were included in our models, the racial difference in receiving ODX testing among node positive women was attenuated and no longer statistically significant (aRR: 0.54, p=0.006 vs. aRR: 0.68, p=0.172). SES factors appeared to partially explain the observed racial difference in receiving ODX testing, but sample size constraints limited our ability to fully control for SES factors. Because ODX testing in node positive women (outside of clinical trial settings) is not aligned with current medical guidelines, Black women were actually receiving more guideline concordant care compared to non-Black women.

Second, ODX testing in node positive patients may be ordered and covered within the purview of clinical trials. The RxPONDER trial has 23 recruitment sites across NC, and during qualitative interviews, several providers discussed their infrequent ordering of ODX testing in node positive patients, except in the case of clinical trial enrollment. Given known disparities in minority participation in clinical trials [1, 2], we may be observing a racial difference in ODX uptake that is

mediated by differential clinical trial enrollment. Future studies should examine this explicitly, as clinical trial enrollment may be a potential intervention for ameliorating racial variation in the uptake of new technologies early in adoption.

Associations of Covariates with ODX Use

In total, fewer than half of women who were eligible for ODX per current guidelines received the test. In addition to race, associations were detected between covariates and receiving ODX testing, including (1) tumor characteristics, (2) age, and (3) year of diagnosis. First, among node negative patients, women with medium-sized (2-5 cm), grade 2- 3 grade, and PR+ tumors were more likely to receive ODX testing. One potential explanation for this finding may include the role that clinical uncertainty plays in the use of ODX for chemotherapy decision-making. During qualitative interviews, oncologists discussed using ODX test results to reduce uncertainty in treatment decisions. In circumstances when the tumor had particularly favorable characteristics or seemingly aggressive characteristics, providers expressed being less likely to order ODX testing, as they were already fairly certain that chemotherapy would not or would be beneficial, respectively.

Second, young age played a role in ODX test receipt in node positive women: qualitative interviews revealed that providers felt less certain of the validity for ODX among young women. In particular, among node positive patients, providers discussed ordering ODX testing more often among women with comorbidities or frailty due to older age to see if they could safely forgo adjuvant chemotherapy. Because young women tend to be healthier, providers discussed being less likely to order ODX and more likely to move forward with guideline-concordant chemotherapy among node positive patients.

Third, among node positive patients, year of breast cancer diagnosis influenced ODX uptake: This aligns with Roger's theory of diffusion [3], and previous work [4] demonstrating that the use of genetic tests increases over time, following an s-shaped curve. Node positive patients were more likely to receive ODX testing in 2012/2013 compared to 2008. Reasons we did not see the same effect in node negative patients may be due to timing of insurance coverage and guideline incorporation, as the first set of women enrolled in CBCS-III was in 2008. By this time, ODX testing was widely covered and had been included in NCCN and ACS guidelines among node negative

patients. This finding also aligns well with qualitative findings, in which providers described the barriers of ODX testing as being ameliorated over time.

Additional Qualitative Factors That May Influence ODX Use

Provider interviews yielded a rich set of multilevel factors that influenced ordering ODX testing for adjuvant chemotherapy decision-making.

Organizational Level Factors

Organizational level factors appeared to be particularly influential in ordering ODX. Silos between surgical oncology, medical oncology, and pathology departments created barriers for ordering ODX in a coordinated, timely fashion. While this did not appear to dissuade ordering ODX testing, providers reported that these silos resulted in delays that were not clinically important, but may impact patients in terms of anxiety. Multidisciplinary teams that met to discuss patients during tumor board were viewed as easing the coordination of ordering ODX testing for patients. Furthermore, some providers delegated a nurse to order ODX tests. Genomic health marketing was often credited for providing up-to-date clinical evidence regarding ODX testing as well. Streamlined processes in conjunction with easy online ordering and training through Genomic Health seemed to facilitate ODX test use.

Providers also discussed how insurance coverage and supportive clinical guidelines have facilitated test use over time. Again, this further explains why we may see differential patterns of ODX testing across nodal status. While currently, insurance policies and coverage support ODX testing for node negative disease, this is not the case for node positive disease. For these reasons, providers discussed lower use of ODX testing in patients with node positive disease, unless they were looking for additional information supporting non-use of adjuvant chemotherapy (e.g., in a frail patient) or were ordering ODX testing in the context of a clinical trial. Interestingly, descriptive analyses in our quantitative work suggested that the ODX testing has increased over time for node positive patients to levels similar to those among node negative patients.

In addition to favorable guidelines and coverage, provider typically referenced Genomic Health as a facilitator for ordering ODX tests. Genomic Health was mentioned by all but one provider as providing educational materials, training, easy online resources, and help with insurance coverage.

This support was often referenced as a facilitator for ordering ODX tests among providers.

Interpersonal and Social Usage Factors

Providers discussed how ODX ordering practices among their peers, especially referring providers or others on their care team, influenced how they order the test. For example, some surgical oncologists ordered tests or discussed ODX testing with patients due to concerns that peer medical oncologists may not offer the test to patients who may benefit from ODX risk results. Other surgical oncologists discussed never ordering ODX testing, as they defer to medical oncology. Furthermore, providers discussed norms around ordering ODX tests within their clinics with the acknowledgement that not all provider groups order the ODX test and use the ODX test results the same way. This suggests a role for interpersonal factors and social usage of ODX testing in whether providers accept ODX testing within particular clinical situations (e.g., node positivity). Furthermore, it became apparent that variation in ODX testing exists across providers and health centers. Providers discussed that norms, especially around ODX testing in node positive patients varies by region, clinics, and individual providers. This information demonstrates why it was necessary in our quantitative analyses to control for provider level clustering.

Intrapersonal-Level Factors

Providers described overall positive attitudes towards ODX testing compared to alternative gene expression profiling tests, such as Mammaprint, citing greater evidence for ODX testing including its inclusion in clinical guidelines. Here again, we see how time may influence ODX uptake, as it takes time to generate enough evidence for its subsequent incorporation into insurance policies and clinical guidelines. Providers also perceived patient knowledge (including misconceptions) and difficulty explaining the complexity of tumor gene expression profiling as challenges to incorporating ODX testing into clinical care for patients. Providers discussed their personal communication styles for describing ODX testing and results to patients: While these communication results fall outside the aims of this dissertation, communication styles for describing the ODX test and test results were often discussed.

ODX Test Results and Adjuvant Chemotherapy Decision-Making

Overall, we did not find racial variation in adjuvant chemotherapy decision-making among

women who received ODX testing. Women in the high-risk group showed a non-significant racial trend, with Black women being more likely to use adjuvant chemotherapy compared to white women; however, our sample size is too small to reach a clear conclusion. Secondary analyses utilizing propensity score analyses showed that Black women were 25% more likely to receive adjuvant chemotherapy in the high risk group in two models. (Appendix 1)

Some previous literature found racial disparities in adjuvant chemotherapy [5-7]; however, our findings are consistent with recent literature that has not observed racial differences [8-10]. There are two potential explanations for the lack of racial differences. First, women receiving ODX testing may differ from women who do not receive ODX testing. So, while adjuvant chemotherapy was not associated with race among our cohort, these results may not generalize to patients who do not receive ODX. Second, our results may reflect literature that has not observed racial differences in adjuvant chemotherapy initiation with or without an ODX test result. Future studies could examine these hypotheses directly.

High and Low Risk Scores and Adjuvant Chemotherapy

Interestingly, we found that the vast majority of women in the high and low risk groups received guideline concordant chemotherapy (i.e., low risk score did not receive adjuvant chemotherapy, high risk score did receive adjuvant chemotherapy). Within the intermediate risk group, about half of women received adjuvant chemotherapy. Risk score distributions across non-Black and Black women were similar; however, Black women tended to have higher risk scores compared to whites in the intermediate risk group. Furthermore, risk scores among node negative and node positive women were similar (Appendix 8).

The high- and low- risk ODX scores present clear adjuvant chemotherapy decisions that cross cut all patient populations. Overall, the vast majority of patients with low risk scores did not receive adjuvant chemotherapy (93.9%); in the high risk group 80.1% received adjuvant chemotherapy. This corroborates qualitative findings that suggested discordant decisions (e.g., patients with low risk scores initiating chemotherapy) occurred less frequently, and typically resulted from patient preferences. Again, this was a rare event, as patient preferences were typically discussed prior to ordering the ODX test. Almost 20% of high-risk patients did not initiate adjuvant

chemotherapy: qualitative data also corroborate this trend, as providers discussed guideline discordant decisions to occur more frequently in the high risk group due to patients “changing their mind” about adjuvant chemotherapy preferences.

Among patients with low ODX risk, higher ODX score, higher tumor grade and being married were independently associated with an increased likelihood of adjuvant chemotherapy initiation. In qualitative interviews, providers discussed ODX as a continuous score, acknowledging the actual risk score (rather than risk group alone) may influence decision-making, though this was more often in the context of the intermediate group. Similarly, higher tumor grade was associated with an increased risk of adjuvant chemotherapy. Among women in the low risk group, being married was also associated with adjuvant chemotherapy initiation, suggesting that social support may lead to higher rates of treatment [11].

Intermediate Risk Group and Adjuvant Chemotherapy Use

Within the intermediate risk group, there is unclear evidence of benefit from adjuvant chemotherapy. Thus, providers and their patients with intermediate risk scores must engage in a more complex decision-making process. No racial differences were observed in chemotherapy initiation within this risk group, and about half of women in this group initiated chemotherapy. In qualitative interviews, providers viewed intermediate risk scores as a major barrier to ODX use. To mitigate this barrier, providers created decision rules for women within this group; these rules varied across providers, but the majority reverted to traditional factors such as tumor characteristics, age, and patient preferences.

In our quantitative analysis, larger tumor size, higher ODX score, and younger age were associated with adjuvant chemotherapy uptake in the intermediate risk group. Young age was associated with adjuvant chemotherapy among the intermediate risk group, aligning with qualitative data where providers questioned the value of ODX testing as they were more likely to move forward with chemotherapy. We also found that lower income was associated with increased chance of receiving chemotherapy. Reasons for this result are unclear, however provider or organizational level factors may play a role. Further research would be necessary to understand how income is related to chemotherapy initiation among women receiving ODX testing.

Policy Relevance

Overall, a complex array of factors influences the uptake of ODX testing and its use for adjuvant chemotherapy decision-making. Fortunately, racial disparities in ODX uptake were not observed in women with node negative breast cancer, nor was adjuvant chemotherapy decision-making in the presence of ODX results associated with race. This suggests that in guideline-concordant applications of ODX testing, women are equally likely to access ODX testing and subsequent adjuvant chemotherapy. Interestingly, Black race was a predictor of lower ODX testing among node positive patients for whom guidelines do not currently recommend the test. One interpretation is that Black women are receiving more guideline-concordant care. Alternatively, newer genetic technologies may be accessed less by Black patients. For the latter, interventions to increase the uptake of new genetic technologies should target minority patients during early adoption of tests. Before developing such interventions, future studies should seek to uncover reasons for the differences. A key to better understanding the source of this variation may lie in examining (1) racial/ethnic disparities in genetic technology access through clinical trials and (2) multilevel factors associated with the uptake of ODX testing across patient populations.

Despite barriers, the uptake of ODX testing represents an example of a successful genetic technology that has reshaped breast cancer care for women with early stage disease. Hopefully, we can apply the lessons learned from patterns of ODX uptake to newly emerging technologies as they are being disseminated to patients across providers and health care settings. In addition, rapidly incorporating these technologies into insurance policies and practices will be critical for policy makers and payers.

Limitations

This section addresses limitations to the current study, and offers recommendations for future studies that address these shortcomings.

Aims 1 and 2

Five main limitations arose in our analytical models for Aims 1 and 2. First, we were unable to include patient preferences in either primary analysis. Ideally, the IOM definition of health disparities would have us control for patient preferences, however no such measures were available. It is

possible that patient preferences for ODX testing and adjuvant chemotherapy initiation vary by race, acting as mediating variables. If so, our estimates for the effect of being Black on ODX test receipt and on adjuvant chemotherapy initiation may be biased. This is possible, as evidence suggests that patient preferences vary by race [12]. In this scenario, instead of describing the direct of effect of race on ODX uptake and adjuvant chemotherapy in the modified Poisson models, we would be estimating the reduced form effect of race on ODX test receipt. Given that racial variation did not occur in adjuvant chemotherapy initiation, we would expect that patient preferences across racial groups were either similar or did not greatly influence adjuvant chemotherapy initiation.

Second, qualitative results demonstrated the importance of organizational and provider level factors on the receipt of ODX testing, however we were unable to control for these factors in our quantitative analyses. Future studies should utilize data sets linked to organizational (e.g., American Hospital Association) and provider level data (e.g., American Medical Association).

Third, our definition of ODX testing assumes that if a patient received ODX testing, the results would reside in pathology or medical records. If this assumption was false, we would underestimate the proportion of women who received ODX. While this is possible, uptake of ODX testing was consistent with that reported in other studies [13, 14]. Furthermore, if we are missing some data on ODX test uptake, it is likely missing at random, and given our dichotomous dependent and independent variables, the effect of misclassification would likely be non-differential.

Fourth, data for income and employment were often missing, which was particularly an issue in Aim1. Studies indicate data on SES are not missing at random for women [15], creating potential bias. Thus, we created categories for missing income and employment data in Aim 1 and 2 (however these categories were dropped from Aim 2 analysis). Furthermore, race, ODX test receipt, and adjuvant chemotherapy initiation did not vary between the analytic sample and individuals with missing data.

Finally, despite analyzing data from one of the largest longitudinal breast cancer studies of Black women, our multivariate analyses were underpowered. To gain power, we also used propensity score analyses to control for baseline characteristics. These models produced similar associations between race and our dependent variables. This strengthens the conclusion that, despite low power,

we have captured existing racial disparities, controlling for clinical and treatment characteristics (though power is still limited in the Aim 2 for the high risk group model). However, one restricted propensity weighted model and one restricted propensity matched model found a statistically significant increased likelihood of adjuvant chemotherapy initiation among Black women compared to non-Black women with high ODX risk scores. Using national datasets that are linked to ODX test uptake would not only increase sample size and power, but also generalizability, as our data were from a single Southeastern state. Furthermore a larger sample size would allow us to include not only race, but also ethnicity related information.

Aim 3

The main goal of this aim was to understand multilevel barriers and facilitators to ODX uptake in clinical practice. One advantage of using qualitative methods is the richness and depth of the data; however, this comes with a tradeoff for lower generalizability. Using purposive recruitment, it is likely that providers who agree to participate in this study differ from those who declined participating. Moreover, we tried to elicit providers' opinions on why patients' ODX uptake and chemotherapy initiation may differ by race or SES; however, providers were reluctant to discuss race as a factor associated with treatment decision-making. Our results be vulnerable to social desirability biases. More directed techniques (e.g., vignettes) could attempt to better isolate provider perceptions or biases on ODX uptake, adjuvant chemotherapy initiation, and race.

Future Directions

Understanding how genomic technologies influence racial disparities in cancer care processes and outcomes will be imperative moving forward in the era of precision medicine. This study provides a foundation for future research, including:

1. Extending research to other genomic tests used in cancer care (e.g., Oncotype DX colon assay).
2. Extending research to the use of genomic testing outside of cancer care (e.g., genetic testing for drug response, health risks, and carrier status).
3. Informing decision-makers (policymakers and payers) about reimbursement for genomic tests under different insurance structures (e.g., high deductible health

plans)

4. Developing interventions (e.g., genetic counseling, educational) that increase access to genetic/genomic testing
5. Evaluating interventions that optimize how ODX test results are communicated and used in clinical practice.
6. Developing decision tools to help patients and providers (including genetic counselors) make decisions around genetic/genomic testing that align with patient values
7. Helping health care organizations develop infrastructures that facilitate access to genetic tests that improve the process and outcomes of care for their patients

Additionally, several more specific research studies would extend this dissertation research focusing on (1) multilevel factors associated with ODX test uptake, (2) the interaction of time and organizational barriers to genetic technology use, (3) leveraging national data sets, and (4) racial differences in adjuvant chemotherapy *completion*.

Qualitative findings demonstrated the importance of multilevel factors on ODX test uptake. Future studies could investigate how provider and organizational level variation affects ODX test uptake. Using large linked data sets would provide a good platform for conducting these analyses. For example, the Integrated Cancer Information and Surveillance System (ICISS) data provide multi-payer claims that can be linked with SEER data as well as provider and organizational level factors. Leveraging powerful data sets such as ICISS to conduct multilevel analyses would provide valuable information about the diffusion of this technology into clinical care. Accounting for provider and organizational variation, as well as factors such as the use of multidisciplinary teams and clinical trial enrollment (e.g., RxPONDER and TAILORx) would be interesting organizational factors to consider.

Another important qualitative finding was that organizational barriers appeared to dissipate over time, suggesting the importance of interventions during the early adoption of new genetic technologies. More investigation focusing on organizational practices over time would provide additional insights in how the use of these technologies changes over time. Prospective data collection on how structures for ordering and using new technologies would better elucidate this

process and identify targets for interventions that facilitate the incorporation of genetic technologies into clinical practice. Furthermore, while this dissertation uses one of the largest Black breast cancer cohort studies in the nation, sample size remains a limitation. Aim 1 and 2 analyses could be reconstructed using larger datasets, such as SEER-Medicare data linked with Genomic Health data. The National Cancer Institute is currently conducted such analyses, and results from their studies will provide the power required to investigate associations between multilevel covariates and outcomes [16].

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APPENDIX 1: PROPENSITY SCORE ANALYSES

Background

In cases where there are large differences between treatment groups on observed covariates, usual multivariate techniques may be inadequate for addressing unbalanced characteristics of the groups. We can account for multiple observed covariates across two groups (i.e., Black and White women) using a single measure, the propensity score. Propensity score models provide unbiased average treatment effects, assuming no unmeasured confounding [1]. The propensity score is the probability of being treated (e.g., being Black) given a set of covariate values. This score is particularly helpful when there is limited sample size: Propensity score models not only decrease bias, but also increase precision when properly specified. The two most common approaches to propensity score application are weighting and matching [2, 3].

Propensity score weighting is appealing since it allows you to retain your full sample. However, average treatment effects can vary across propensity score weighted and matched models if propensity score overlap is insufficient and there are extreme observations [4]. In such cases weighted models may give a large amount of influence to outlier values, which may or may not be representative of the population of interest. Because of these concerns and potential differences between weighted and matched estimates, we conducted both propensity score-weighted models and propensity score matched models and compared results across models. This ensures that our propensity-weighted models were not biased due to sensitivity to extreme observations.

Because we had limited power in some of our primary models, these propensity models allowed us to control for covariates using one measure rather than multiple covariates, increasing power to detect clinically significant differences in the association between race with ODX testing receipt and adjuvant chemotherapy initiation. Thus, these models acted as sensitive analyses for our primary models, which used modified Poisson regression techniques with sandwich standard errors.

Methods

We used STATA commands and methods created by Lunt for the implementation of propensity score weighting and matching [5].

Covariate Imbalance

Literature demonstrating racial differences in tumor biology and overall health among breast cancer patients suggest that propensity score models may be a tool for controlling underlying differences between Black and White women [6]. We confirmed that imbalances existed in our data by baseline covariates across Black and White women. Results demonstrated that covariates were imbalanced across racial groups in Aims 1 and 2 (Table 1-5).

Calculating the Propensity Score

We used a logistic regression to model the association between tumor and clinical characteristics with race. The Hosmer-Lemeshow goodness of fit test was used to test the specification of the logistic models used to predict the propensity scores. All models passed this specification test ($p>0.05$). We then calculated the linear predictor (log odds of the propensity score) to compare the distributions of the propensity scores across Black and White women (Figures 1-5: Distribution of Log Odds of Propensity Scores across Racial Groups). The calculated propensity scores and linear predictors were then used for propensity weighted and matched models.

Weighted Propensity Score Models

We used standardized mortality/morbidity ratio (SMR) weights to facilitate a counterfactual estimate of the average treatment effect [4]. Using SMR weights, we estimated the outcome of interest among Black patients, assuming that they had the characteristics of White patients. Next, we rechecked the balance of the covariates with the SMR weights: for each model, all covariates (i.e., year of diagnosis, tumor size, tumor grade, progesterone receptor status, mastectomy, age at diagnosis, number of comorbidities) included in the propensity scores were balanced with the propensity score weights (results not shown). Then we regressed race on our outcome variables using the propensity score weight. In SMR weighted models, patients treated against prediction are included and are assigned a particularly small or large propensity weight: these extreme weights often result from unmeasured confounding and can lead to biased estimates. Thus, we excluded them from the analysis using trimming: we trimmed the 5^{th} percentile of observations with particularly large or small propensity scores and recalculated the average treatment effect (excluded patients with propensity scores outside of the 5^{th}-95^{th} percentile).

Matched Propensity Score Models

We used Greedy matching techniques for our propensity score-matched analysis. This technique matches a set of Black women's propensity scores with a set of White women's propensity scores: Greedy matching uses the best match available; once a match is made, it is not reconsidered. Best matches are made until there are no more possible pairings [7]. Parson's Greedy matching technique first matches on 5 digits, then 4 digits down to 1 digit. One potential downfall to this approach is that match quality may decrease after a certain point, because the technique insisted on finding a match for each observation with Black race. We set a caliper of 0.1; this excludes poor matches from the analysis and improves the overall quality of matching in our analysis [8]. We then rechecked the balance of the covariates after setting the caliper, and we found our covariates to be balanced (Table 1-5). Then we regressed race on our outcome variables using matching with the 0.1 caliper.

Results

Aim 1

Because both weighted and matched models yielded similar results, we present propensity weighted analyses as this technique retains the full sample of women. Racial differences in ODX testing receipt were not found among women with node negative disease, however differences were found among women with node positive disease. Black women were 13% less likely to receive ODX testing compared to White women (ATE=-0.13, 95% CI= -0.22, -0.030 p=0.01) (Table 6).

Aim 2

Propensity score weighted and matched models yielded different results. Likely, weighted models were vulnerable to extreme observations. Racial differences in adjuvant chemotherapy initiation were not found among women across ODX risk groups in propensity score matched models (Table 7). Racial differences in adjuvant chemotherapy initiation were uncovered among women in the high risk group in our propensity score weighted model (Table 8). AA women in the high risk group were 25% more likely to initiate adjuvant chemotherapy compared to non-AA women (ATE=0.25, 95% CI= 0.051, 0.46, p=0.015.

Conclusions

Results from our propensity score analyses corroborated findings in our primary modified Poisson regression models for both Aims 1 and 2: While there were no racial differences in ODX testing receipt among node negative patients, Black women were less likely to receive ODX testing compared to White women with node positive disease. There were no racial differences in adjuvant chemotherapy initiation across ODX risk groups. Furthermore, propensity score weighted and matched models yielded similar findings across all analyses.

Propensity weighted models for the high risk group in Aim 2 suggests that AA women are 25%-28% more likely to receive adjuvant chemotherapy compared to non-AA women. Racial differences are only observed after trimming and restricting results: this suggests that among this select subpopulation of patients, AA women are more likely to receive guideline concordant chemotherapy compared to non-AA women. Overall, results from these models suggest decreased ODX receipt among AA women compared to non-AA women with node positive breast cancer, but not node negative breast cancer. Furthermore, race does not seem to influence adjuvant chemotherapy initiation; however, AA women may be more likely to initiate adjuvant chemotherapy in the high-risk group.

Limitations

Propensity score models can only balance the “treatment” groups by observed variables, which are included in the model. Furthermore, propensity score analyses are as good as the variables used in the propensity score estimation, that is, the treatment variable, race, must largely be a function of the observed characteristics. Finally, propensity score models assume balance on unmeasured confounding, which we cannot confirm.

Tables

Table 1. Means by race and standardized differences between baseline characteristics by race demonstrating differences in covariates across racial groups with node negative breast cancer in Aim 1 before and after propensity score weighting. Standardized differences measure effect sizes between two groups independent of sample size. Yellow indicates imbalance across racial groups.

Aim 1. Node Negative: Baseline Characteristics: unbalanced without propensity scores				**Baseline Characteristics: balanced with propensity score weighting**		
Variable	Mean in AA	Mean in non-AA	Standardized Difference	Mean in AA	Mean in non-AA	Standardized Difference
Age <50	0.4	0.45	-0.1	0.38	0.38	0.016
Large tumor size	0.03	0.03	0.03	0.03	0.03	0.024
Small tumor size	0.69	0.78	-0.197	0.7	0.69	0.013
Medium tumor size	0.28	0.19	0.193	0.27	0.28	-0.024
Tumor grade 1	0.31	0.38	-0.163	0.48	0.5	-0.034
Tumor grade 2	0.48	0.45	0.052	0.21	0.19	0.041
Tumor grade 3	0.21	0.16	0.131	0.31	0.31	0.001
PR Positive	0.81	0.9	-0.237	0.82	0.84	-0.062
Mastectomy	0.34	0.39	-0.109	0.33	0.33	0.003
# Comorbidities	1.18	0.6	0.607	1.2	1.33	-0.137
Diagnosis 2008	0.1	0.1	-0.006	0.1	0.1	0.025
Diagnosis 2009	0.18	0.21	-0.091	0.18	0.17	0.024
Diagnosis 2010	0.24	0.25	-0.028	0.24	0.25	-0.022
Diagnosis 2011	0.28	0.22	0.123	0.28	0.29	-0.013
Diagnosis 2012	0.18	0.21	-0.066	0.19	0.19	-0.005

Table 2. Means by race and standardized differences between baseline characteristics by race demonstrating differences in covariates across racial groups with node positive breast cancer in Aim 1 before and after propensity score weighting. Standardized differences measure effect sizes between two groups independent of sample size. Yellow indicates imbalance across racial groups.

Aim 1. Node Positive: Baseline Characteristics: unbalanced without propensity score weighting	**Baseline Characteristics: balanced with propensity score weighting**

Variable	Mean in AA	Mean in non-AA	Standardized Difference	Mean in AA	Mean in non-AA	Standardized Difference
Age <50	0.55	0.58	-0.063	0.52	0.5	0.044
Large tumor size	0.02	0.02	-0.023	0.02	0.02	0.016
Small tumor size	0.44	0.52	-0.167	0.44	0.43	0.007
Medium tumor size	0.54	0.46	0.173	0.54	0.55	-0.011
Tumor grade 1	0.17	0.26	-0.205	0.17	0.22	-0.117
Tumor grade 2	0.44	0.50	-0.116	0.44	0.44	-0.013
Tumor grade 3	0.38	0.24	0.309	0.39	0.34	0.118
PR Positive	0.79	0.93	-0.404	0.79	0.8	-0.044
Mastectomy	0.49	0.55	-0.126	0.48	0.49	-0.028
# Comorbidities	0.98	0.56	0.437	1.02	1.11	-0.096
Diagnosis 2008	0.13	0.13	-0.001	0.14	0.11	0.082
Diagnosis 2009	0.24	0.18	0.152	0.25	0.27	-0.027
Diagnosis 2010	0.19	0.23	-0.105	0.2	0.2	0.006
Diagnosis 2011	0.25	0.25	0.009	0.27	0.28	-0.023
Diagnosis 2012	0.13	0.22	-0.220	0.14	0.15	-0.024

Table 3. Means by race and standardized differences between baseline characteristics by race demonstrating differences in covariates across racial groups with low ODX risk tumors in the Aim 2 sample before and after propensity score weighting. Standardized differences measure effect sizes between two groups independent of sample size. Yellow indicates imbalance across racial groups.

Aim 2. Low ODX Risk Group: Baseline Characteristics: unbalanced without propensity score weighting				**Baseline Characteristics: balanced with propensity score weighting**		
Variable	Mean in AA	Mean in Non-AA	Standardized diff.	Mean in AA	Mean in Non-AA	Standardized diff.
Node Positive	0.15	0.13	0.05	0.12	0.15	-0.073
Age < 50	0.43	0.5	-0.14	0.41	0.4	0.023
ODX Score	11.32	11.65	-0.08	11.41	11.5	-0.022
Small tumor	0.73	0.75	-0.04	0.73	0.74	-0.01
Medium tumor	0.27	0.25	0.04	0.27	0.26	0.01
Large tumor	0	0	.	0	0	.
Tumor grade 1	0.62	0.53	0.18	0.29	0.29	-0.002
Tumor grade 2	0.3	0.41	-0.24	0.63	0.61	0.037
Tumor grade 3	0.08	0.05	0.1	0.08	0.1	-0.069
PR Positive	0.97	0.98	-0.03	0.97	0.97	-0.011
Mastectomy	0.34	0.4	-0.13	0.33	0.34	-0.022
# Comorbidities	1.06	0.59	0.55	1.08	1.12	-0.046
Diagnosis	0.16	0.09	0.22	0.16	0.14	0.068

2008 Diagnosis						
2009	0.19	0.19	-0.01	0.2	0.2	-0.016
Diagnosis 2010	0.15	0.26	-0.28	0.15	0.16	-0.007
Diagnosis 2011	0.27	0.25	0.04	0.28	0.25	0.06
Diagnosis 2012	0.2	0.21	-0.02	0.21	0.25	-0.098

Table 4. Means by race and standardized differences between baseline characteristics by race demonstrating differences in covariates across racial groups with intermediate ODX risk tumors in the Aim 2 sample before and after propensity score weighting. Standardized differences measure effect sizes between two groups independent of sample size. Yellow indicates imbalance across racial groups.

Aim 2. Intermediate ODX Risk Group: Baseline Characteristics: unbalanced without propensity score weighting				**Baseline Characteristics: balanced with propensity score weighting**		
Variables	Mean in treated	Mean in Untreated	Standardized diff.	Mean in treated	Mean in Untreated	Standardized diff.
ODX Score	22.97	22.07	0.248	23.01	23.34	-0.089
Node Positive	0.1	0.2	-0.294	0.09	0.09	0
Age < 50	0.4	0.49	-0.165	0.36	0.38	-0.038
Grade 2	0.53	0.57	-0.094	0.51	0.51	0.005
Grade 3	0.14	0.22	-0.203	0.15	0.2	-0.14
Grade 1	0.33	0.21	0.281	0.34	0.29	0.116
PR Positive	0.78	0.92	-0.395	0.78	0.83	-0.147
Mastectomy	0.26	0.43	-0.358	0.27	0.27	-0.003
# Comorbidities	0.92	0.46	0.575	0.97	1	-0.034
Diagnosis 2008	0.08	0.13	-0.163	0.09	0.11	-0.051
Diagnosis 2009	0.19	0.23	-0.09	0.21	0.18	0.073
Diagnosis 2010	0.25	0.23	0.043	0.27	0.27	0
Diagnosis 2011	0.29	0.19	0.247	0.31	0.33	-0.03
Diagnosis 2012	0.11	0.22	-0.286	0.12	0.12	-0.003

Table 5. Means by race and standardized differences between baseline characteristics by race demonstrating differences in covariates across racial groups with high ODX risk tumors in the Aim 2 sample before and after propensity score weighting. Standardized differences measure effect sizes between two groups independent of sample size. Yellow indicates imbalance across racial groups.

Aim 2. High ODX Risk Group: Baseline Characteristics: unbalanced without propensity score weighting				**Baseline Characteristics: balanced with propensity score weighting**		
Variables	Mean in AA	Mean in non-AA	Standardized diff.	Mean in AA	Mean in non-AA	Standardized diff.
Node Positive	0.08	0.07	0.062	0.08	0.06	0.078
Age < 50	0.5	0.53	-0.065	0.5	0.63	-0.246
ODX Score	39.13	41.4	-0.246	39.13	39.83	-0.076
Small tumor	0.54	0.77	-0.477	0.54	0.79	-0.523
Medium tumor	0.46	0.23	0.477	0.46	0.21	0.523
Grade 2	0.25	0.17	0.202	0.25	0.18	0.169
Grade 3	0.71	0.77	-0.13	0.71	0.71	-0.007
Grade 1	0.04	0.07	-0.109	0.04	0.11	-0.29
PR Positive	0.63	0.63	-0.017	0.63	0.76	-0.271
Mastectomy	0.42	0.47	-0.099	0.42	0.32	0.199
# Comorbidities	1.33	0.67	0.664	1.33	1.66	-0.323
Diagnosis 2008	0.17	0.17	0	0.17	0.11	0.144
Diagnosis 2009	0.13	0.2	-0.201	0.13	0.11	0.039
Diagnosis 2010	0.25	0.23	0.038	0.25	0.23	0.056
Diagnosis 2011	0.38	0.23	0.306	0.38	0.48	-0.224
Diagnosis 2012	0.08	0.17	-0.249	0.08	0.07	0.03

Table 6. Average treatment effect (restricted and trimmed) of AA race compared to non-AA race on ODX test receipt among node negative and node positive patients.

	Treatment Effect of Race on ODX use with PS Weighting: Restricted & Trimmed					
	Node Negative			Node Positive		
ODX	**Average Treatment Effect**	**P>|t|**	**[95% Conf. Interval]**	**Average Treatment Effect**	**P>|t|**	**[95% Conf. Interval]**
AA (v. non-AA)	-0.068	0.060	-0.14, 0.0029	-0.13	0.011	-0.22, -.030
constant	0.48	<0.001	0.44, 0.53	0.27	<0.001	0.20, 0.35

Table 7. Aim 2. Average treatment effects from the propensity matched models with restriction and trimming. (ATE=average treatment effect, p=p-value, CI= Confidence Interval)

AIM 2.	**Propensity Matched Models**		
LOW RISK	**ATE**	**p**	**95% CI**
Black	0.014	0.765	-0.076, 0.10
Constant	0.083	0.008	0.022, 0.14
INTERMEDIATE RISK			
Black	-0.044	0.675	-0.26, 0.17
Constant	0.46	<0.001	0.32, 0.59
HIGH RISK			
Black	0.29	0.040	0.015, 0.56
Constant	0.74	<0.001	0.58, 0.91

Table 8. Aim 2. Average treatment effects from the propensity weighted models with restriction and trimming. (ATE=average treatment effect, p=p-value, CI= Confidence Interval)

AIM 2.	**Propensity Weighted Models**		
LOW RISK	**ATE**	**p**	**95% CI**
Black	0.0036	0.92	-0.066, 0.073
Constant	0.071	0.001	0.029, 0.11
INTERMEDIATE RISK			
Black	-0.0356	0.71	-0.23, 0.16
Constant	0.46	<0.001	0.35, 0.58
HIGH RISK			
Black	0.25	0.015	0.051, 0.46
Constant	0.75	<0.001	0.54, 0.95

Figures

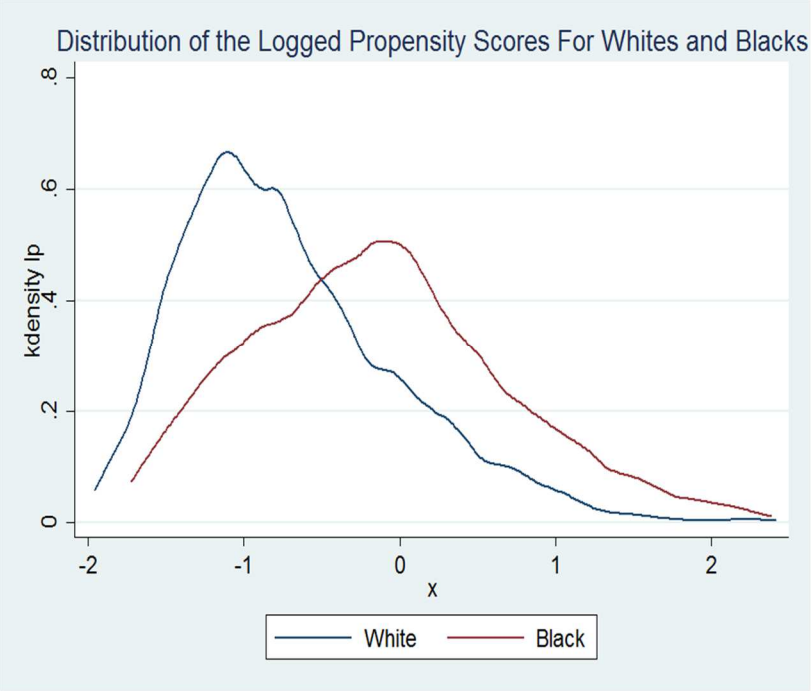

Figure 1. Propensity weights by race (White=non-AA, Black=AA) among node negative patients in Aim 1.

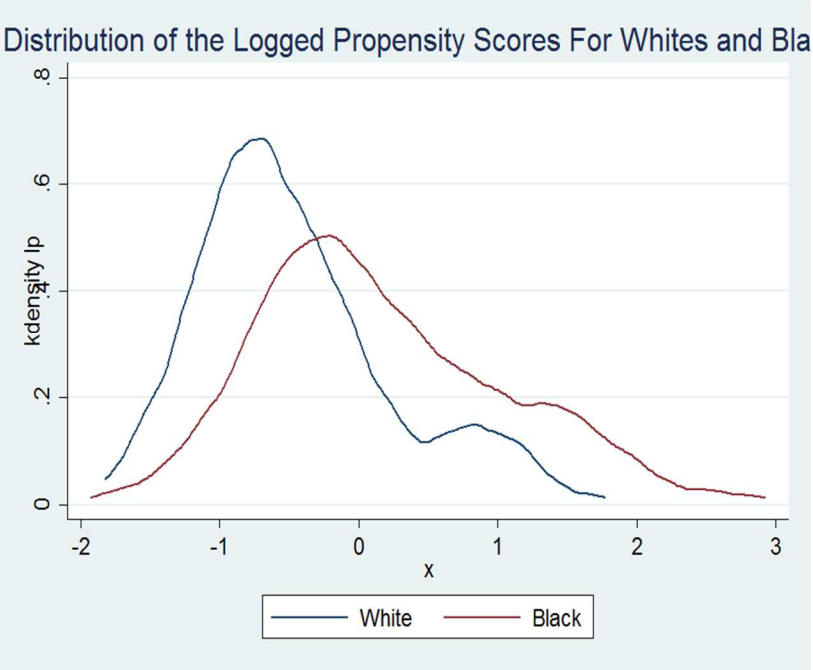

Figure 2. Aim 1. Propensity scores by race (White=non-AA, Black=AA) among node positive.

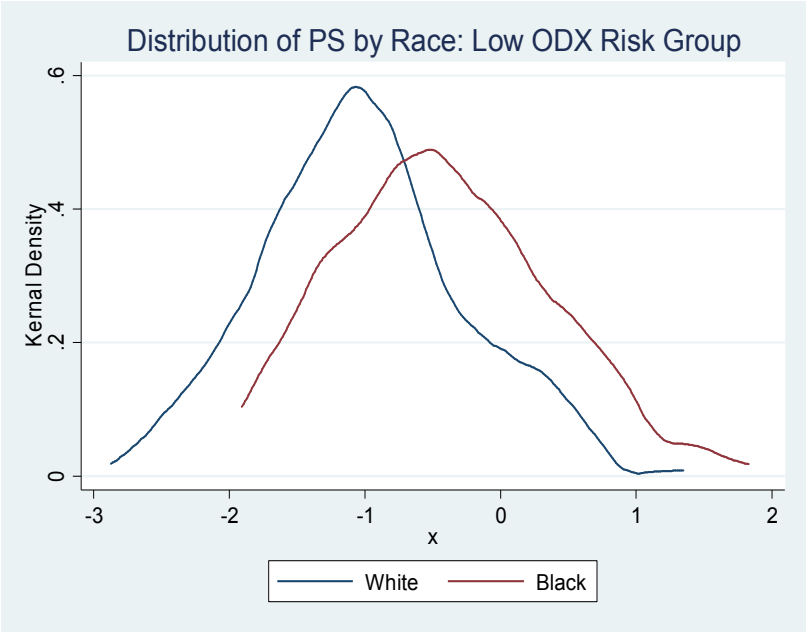

Figure 3. Aim 2: Propensity scores by race (White=non-AA, Black=AA) among women with low ODX risk scores.

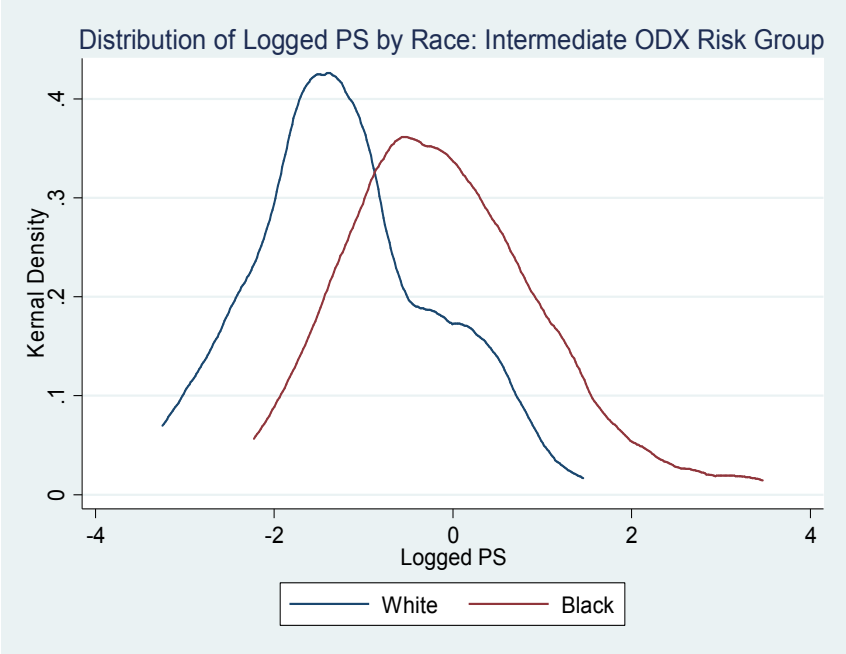

Figure 4. Aim 2: Propensity scores by race (White=non-AA, Black=AA) among women with intermediate ODX risk scores.

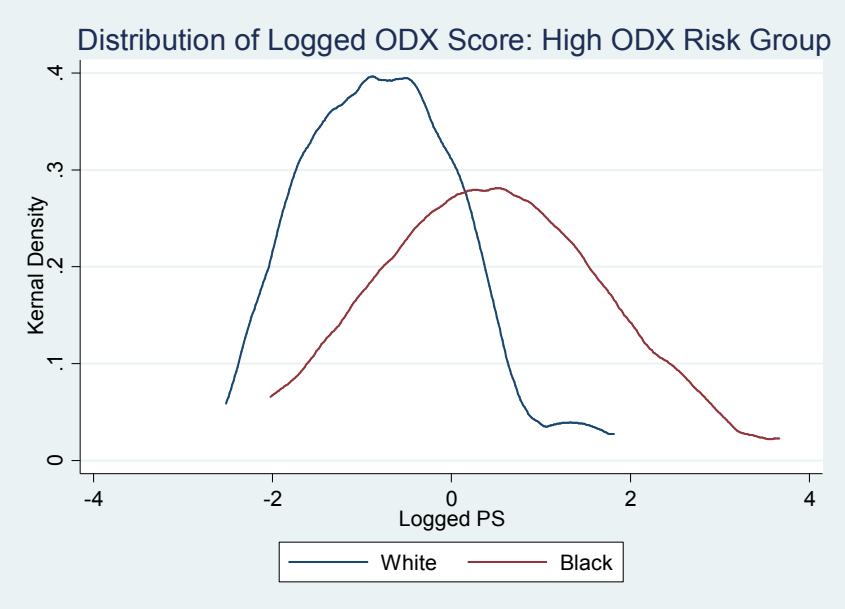

Figure 5. Aim 2: Propensity scores by race (White=non-AA, Black=AA) among women with high ODX risk scores.

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APPENDIX 2: RECRUITMENT LETTER

[Date]

Dear [Provider Name]:

I am a PhD student from the Department of Health Policy and Management at School of Public Health. For my dissertation, I am collaborating with faculty from my Department, as well as oncologists from the Lineberger Comprehensive Cancer Center (including Dr. Katie Reeder-Hayes) to better understand how Oncotype DX is being used by oncologists to make treatment decisions when caring for women with breast cancer. We are reaching out to medical and surgical oncologists, such as you, who have expertise and experience with breast cancer patients. We seek your insights into the ways Oncotype DX testing is being used in clinical practice. We hope that you would be willing to complete a brief questionnaire and participate in a 30-minute phone interview to provide your insights and to support the work of a UNC doctoral student. If you see at least five breast cancer patients a week (to establish care, undergo treatment, for follow-up, etc) and are interested in participating, please simply reply to this email. Upon your reply, we will schedule a time for the interview via phone to discuss Oncotype DX; we would also provide a link to the brief (less than 5 minute) questionnaire that asks for descriptive information about you and your practice. As a token of our appreciation for your participation in this study, you would be offered a $100 VISA gift card. If you have any questions, please feel free to contact me by email (mclarker@unc.edu).

Thank you in advance for your time and consideration.

Best regards,

Megan Roberts

Megan Roberts

CCEP Pre-doctoral Fellow

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Chapel Hill, NC 27599-7411

717.448.3247

mclarker@unc.edu

APPENDIX 3: INFORMED CONSENT AND SURVEY

Before completing this brief survey, you must provide your informed consent below. Please read the information below: After you review the information below, you will be asked whether or not you voluntarily agree to participate in the study. The survey should take no more than 5 minutes to complete.

University of North Carolina-Chapel Hill
Written Consent to Participate in a Research Study
Adult Participants: Oncologists
Social Behavioral Form

Consent Form Version Date: March, 11 2014

Title of Study: Understanding racial disparities in the diffusion of Oncotype DX in breast cancer
Principal Investigator: Megan Roberts
UNC-Chapel Hill Department: Health Policy and Management
Phone number: 717.448.3247
Co-Investigators: Morris Weinberger, Stephanie Wheeler, Katie Reeder-Hayes, Stacie Dusetzina, Michaela Dinan
Funding Source and/or Sponsor: CCEP Pre-Doctoral Fellowship, UNC Lineberger Comprehensive Cancer Center, Megan Roberts
Study Contact telephone number: 717.448.3247
Study Contact email: mclarker@unc.edu

Information about this study

The purpose of this study is to understand how oncologists use Oncotype DX testing to help make treatment decisions for breast cancer patients. We will interview breast medical and surgical oncologists about this topic. For this study, we are interested in what you think about the benefits and challenges of Oncotype DX testing for providing care to women with breast cancer.
If you decide to participate, you will be one of up to 20 oncologists in this research study. Your involvement will include completing a short (~5 minute) survey and participating in a 30-minute telephone interview. With your permission, the interview will be audiotaped, and the interviewer will take notes on the discussion so that the research team can learn about your thoughts on this topic.

Possible benefits from being in this study

Your participation in this study will increase our understanding of how Oncotype DX may be used to improve cancer care for women with breast cancer. You will be offered a $100 VISA gift card for taking part in this study.

Possible risks from being in this study

The risks and discomforts related to this study are minimal. We will take great care to protect the confidentiality of the information you provide. The audio recordings and notes from the interview will be kept confidential, which means that the information will be kept in a secure, password-protected computer that will be accessed **only** by the principal investigator of the study team. All data will be de-identified.

You will not be mentioned by name in any reports, articles or presentations that result from this study. In the event of publication of this research we will not disclose any personally identifiable information.

Your contact information will be kept confidential as required by law and will be kept in a separate, secured file. Your name and address will only be used to send you the $100 VISA gift card. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when

required by law, you will not be identified by name, address, telephone number, or any other direct personal identifier disclosed outside of the University of North Carolina.

For UNC employees ONLY

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Withdrawing from the Study
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time.

What if you have questions about this study?
You have the right to ask and have answered, any questions you may have about this research. If you have questions, complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

- -

Title of Study: Understanding racial disparities in the diffusion of Oncotype DX in breast cancer

Principal Investigator: Megan Roberts

Participant's Agreement:

Do you voluntarily agree to participate in this research study?

[Drop down menu] YES, NO

Please complete the following brief survey:

1. What is your gender?
    a. Female
    b. Male

2. What is your age? _____

3. What is your race/ethnicity? (circle all that apply)
    a. White
    b. Black
    c. Asian
    d. Hispanic
    e. Native American
    f. Other_____

4. What is your role in patient care?
    a. Medical Oncologist
    b. Surgical Oncologist

5. How many years have you been in practice since completing training (all residency and fellowship training)? _____

6. Among my peers, I am usually the first to try out new medical technologies for clinical care (*including screening technologies, new diagnostic and prognostic tests, and therapeutics*) <strongly disagree, disagree, somewhat disagree, neither agree or disagree, somewhat agree, agree ,strongly agree>

In order for us to better understand the patient population that you serve, please estimate the following:

7. Approximately what percent of your patients are insured by Medicaid? _____%
8. Approximately what percent of your patients have no insurance? _____%
9. In terms of your patients' racial/ethnic background, approximately what percent of your patients are (these figures should add to 100%):
    a. White _____%
    b. Black _____%
    c. Hispanic _____%
    d. Other _____%

10. Estimate the percentage of <u>your patients</u> who have breast cancer _____%

11. Estimate how many total breast cancer patients that you see in an average week? _____ per week

12. Estimate the percentage of your breast cancer patients that are hormone receptor positive?_____%

In order for us to better understand the practice in which you serve, please estimate the following about your practice setting:

13. Describe your practice setting: (select all that apply)
    a. Public
    b. Private
    c. Academic Affiliated
    d. Non-Academic Affiliated
    e. Urban
    f. Rural
    g. Suburban

14. How many other providers in your practice treat breast cancer patients? _____

15. In a given month, estimate how many times you order Oncotype DX for your patients. _____

APPENDIX 4: SEMI-STRUCTURED INTERVIEW GUIDE

Oncology Clinicians—Interview Guide

Oncotype DX Use in Clinical Practice

I. Introduction

Hello, I'd like to thank you for your time and interest in our research project. Your participation is very important to us. My name is Megan Roberts and I'll be talking with you today about the use of the tumor gene-profiling test, Oncotype DX, in the care of early stage breast cancer patients. Your opinions as an oncologist are extremely valuable as we try to better understand factors affecting the use of this test in clinical practice.

I will be audio taping our discussion, because I want to make sure I don't miss anything. I will ultimately summarize the comments of all oncologists that I have interviewed. I want to assure you that your comments will be kept confidential and that nothing you say will be connected with your name or your patients. We are interested in your ideas, comments and suggestions. Please feel free to share your thoughts and talk candidly during the discussion.

II. Personal Attitudes and Beliefs

First, I would like to hear about your personal thoughts about how you use Oncotype DX testing in your own practice.

2. Think about last month, how often would you estimate that you ordered ODX testing for your patients? *
   If NO & surgical oncologist, Start w/ #7.
3. *When you recommend/order the test, at what point* following diagnosis do you typically do so?

4. How do <u>you (your team) decide</u> which of <u>your patients</u> should be offered this test? For whom would you recommend ODX? *
   PROBE IF NECESSARY:
   a. Do you ever use ODX for <u>your node positive patients</u>? Why/why not?
   b. Do you ever use ODX for <u>your patients with DCIS</u>? Why/why not?
   c. Do you ever use ODX for <u>your patients with metastatic disease</u>? Why/why not?
   d. Among <u>your patients</u> who you feel are eligible for this test, which of <u>your patients</u> do you think benefit most from having this test (e.g., clinical characteristics, age, family history, etc.)?

5. Do you discuss with your patient whether they should have Oncotype DX testing? If YES, how do you discuss with your patients whether they should get Oncotype DX testing?
   PROBE IF NECESSARY:
   a. Do your patients ever refuse to get Oncotype DX testing? If so, why?
      i. What role, if any, does cost influence Oncotype DX use for your patients?
         1. IF YES, Do you explicitly discuss costs with your patients?
      ii. What role do <u>patients' preferences</u> play in determine whether or not your patients receive Oncotype DX testing?
         1. Have you noticed any <u>racial, cultural, educational, economic differences</u> in your patients' preferences regarding ODX use?
   b. Are there alternative tests that you believe are more useful for your chemotherapy decision-making? If so, which ones? *

Now, I'd like to transition into discussing how you use the Oncotype DX test result for your patients.

4. How do you discuss the Oncotype DX result with your patient? *
   PROBE:
   a. Do you use the Oncotype DX chart that Genomic Health produces with your patients? If so, what is useful about the presentation of the results? What do you think could be done better?
      i. Do you provide your patient with a copy of the Genomic Health report?
   b. What are the challenges and strengths of using Oncotype DX test results in your treatment decision-making? *
      i. Do you have patients who you worry won't be able to interpret the results? (e.g., age, race, education, etc.)
      ii. Is the waiting time for a test result ever a problem?

5. How does the Oncotype DX risk score influence your (your team's) treatment decision-making?
   PROBE:
   a. How do you handle intermediate risk scores in terms of your decision-making?
   b. Do your patients interpret intermediate risk scores differently? Are there any patterns (e.g., racial or cultural or SES or rural/urban) that seem to influence how the score is used in their decision-making?
   c. Are there times when a patient of yours with a low risk score may still have chemotherapy?
   d. Are there times when a patient of yours with a high-risk score will forgo chemotherapy?

6. Overall, how do you feel that the availability of the Oncotype DX has changed the way that you treat breast cancer? *

Now if we step back for a moment, I would like to talk with you about how Oncotype DX is being used among your colleagues in your practice. First, please think about your colleagues…

III. Interpersonal Factors

7. Now that both surgeons and medical oncologists can order the test, how do you coordinate who orders the test for a given patient?
   a. Do the opinions and practices of other oncologists that you work with influence your use of ODX?
      i. If YES, How? May need to move up for those who do not may ODX orders

IV. Organizational Factors
Now I'd like to discuss practice-level factors…

8. Are there things about the way that your practice is set up that makes using Oncotype DX especially difficult or easy?
   PROBE:
   a. Ordering the test
   b. Filing and getting reimbursement from insurance companies through Genomic Health

9. Has a representative from Genomic Health been to your practice?
   a. IF YES: Have you found the information or services they provide to be helpful? In what way?"

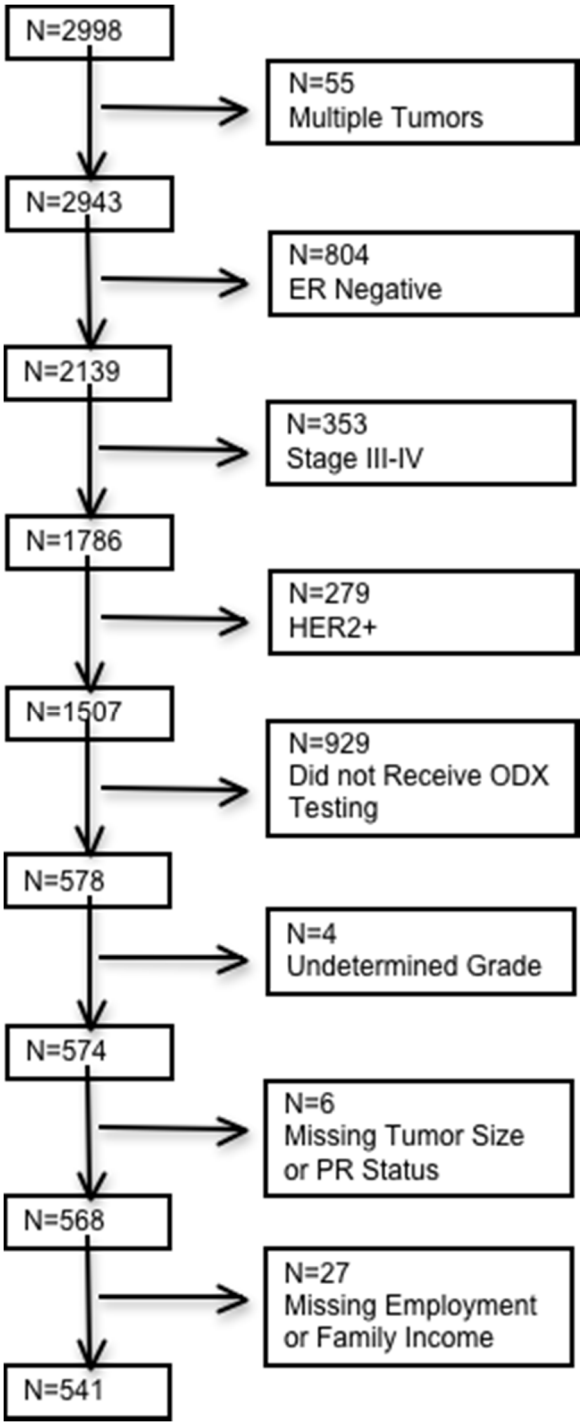
VI. Closing

Thank you very much for participating in these interviews. Within the next two weeks you will receive a thank you letter with $100 visa gift card in appreciation for the time that you took to speak with me today. (Confirm mailing address) (Give providers the opportunity to deny $100 VISA gift card if they choose.)

10. Is there anything else you would like to share with me today? Are there any challenges with or strengths of this test that you feel we haven't discussed?

THANK YOU VERY MUCH!

APPENDIX 5: INCLUSION/EXCLUSION CRITERIA, AIM 2



APPENDIX 6: CODING TEMPLATE

Appendix 6. Final code template and code definitions applied for analysis.

Code Template	Code Definition	Code Frequency
Attitudes/ Perceptions	**Provider attitudes about Oncotype DX use**	
Cost	Cost of ODX as a barrier or facilitator	30
Speed/Timing	Speed or timing of ODX test to result	18
Perceived Patient Preferences	Provider's use of patient preferences in ODX use	57
Biopsy Results	Clinical characteristics that influence ODX use	84
Age	Impact of age on ODX use	48
Uncertainty Around Chemotherapy	Role that uncertainty plays in using ODX	18
Perceived Benefits	Provider perceived benefits for ODX use	27
Comorbidities	Impact of comorbidities on ODX use	22
Geography	Impact of patient or practice geography on ODX us	6
SES	Impact of patients' SES on ODX us	7
Research Gaps	Areas where data are lacking around ODX use and subsequent chemotherapy decisions	13
Alternative Tests	Use or reasons for non-use of other tests as alternatives of ODX	17
Positive Node	Role of positive nodes on ODX use	36
Stories	Clinical vignettes to demonstrate ODX use	12
Barriers	**Factors that prevent providers from using ODX**	51
Facilitators	**Factors that promote providers' use of ODX**	53
Communication	**Provider discussions with patients about ODX**	
Pre-test Communication	Provider discussion with patients about using ODX	59
Post-test Communication	Provider discussion with patients about ODX test result	50
Perceived Patient Knowledge	Provider's belief about patients' understanding of ODX	28
Decision Making	**How provider's use ODX to make chemotherapy decisions**	
Intermediate Risk Group	How providers communicate results and make chemotherapy decisions in the intermediate risk group	35
Discordant Decisions	Why chemotherapy decisions may discord with ODX results	24

Organizational Factors		**How structures and policies influence ODX use**	
	Organization of Practice	How the organization of the practice influences ODX use	47
	Guidelines	How insurance and clinical guidelines influence ODX use	39
	Genomic Health Marketing	How marketing from Genomic Health impacts ODX use	19
Social Usage		**How peers and social norms influence ODX use**	
	Physician Roles	How physicians' roles influence ODX use	47
	Normative Beliefs	Providers' beliefs about how other providers use ODX	17
	Motivation to Comply	How providers' change ODX use based on their beliefs about how other providers use ODX	13
Personal Disposition to Innovativeness		**Providers' tendency to be innovative**	
	New Studies/Clinical Trials	How participating in- or evidence from-clinical trials influences ODX use	18

APPENDIX 7: THEMATIC SATURATION

Appendix 7. Thematic saturation occurred before 15 interviews: No new themes emerged following the seventh interview.

Theme Emergence		Provider Interviews		
Super Codes	Codes	1-5	6-10	11-15
Attitudes/ Perceptions				
	Cost	X		
	Speed/Timing	X		
	Perceived Patient Preferences	X		
	Biopsy Results	X		
	Age	X		
	Uncertainty Around Chemotherapy	X		
	Perceived Benefits	X		
	Comorbidities	X		
	Geography	X		
	SES		X	
	Research Gaps	X		
	Alternative Tests	X		
	Positive Node	X		
	Stories	X		
Personal Disposition to Innovativeness				
	New Studies/Clinical Trials	X		
Communication				
	Pre-test Communication	X		
	Post-test Communication	X		
	Perceived Patient Knowledge	X		
Decision Making				

Intermediate Risk Group	X		
Discordant Decisions	X		
Social Usage			
Physician Roles	X		
Normative Beliefs	X		
Motivation to Comply	X		
Organizational Factors			
Organization of Practice	X		
Guidelines	X		
Genomic Health Marketing	X		
Barriers	X		
Facilitators	X		
# New Themes	**27**	**1**	**0**

APPENDIX 8: ODX RISK SCORES BY LYMPH NODE STATUS

Appendix 8. Kernel density of ODX risk scores by lymph node status.