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Personalized Medicine and the Role of Patient Preferences, Risk Perception and Information Exchange

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Personalized Medicine and the Role of Patient Preferences, Risk Perception and Information Exchange

A dissertation submitted in partial satisfaction of the

Requirements for the degree Doctor of Philosophy

in Health Policy and Management

by

Catherine Claire Chanfreau

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ABSTRACT OF THE DISSERTATION

Personalized Medicine and the Role of Patient Preferences, Risk Perception and Information Exchange

By

Catherine Claire Chanfreau

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2015

Professor Ninez A. Ponce, Chair

There are great expectations in the potential of personalized medicine to improve health outcomes by tailoring treatments to the needs of individual patients. Still, uncertainty remains on the values of these new technologies in the clinical setting. In particular, little is known about how physicians and patients use such information for decision-making, and about the influence of patient preferences, attitudes and information exchange in this process.

This dissertation expands on existing frameworks modeling health behaviors and treatment decisions to conceptualize pathways intervening on treatment decisions. The model studied here is the decision of using chemotherapy in early-stage breast cancer treatment based on a genomic test. This test predicts the risk of tumor recurrence, and helps identify patients at low risk who may avoid potentially unnecessary chemotherapy.

The three studies used data from a retrospective patient survey examining patient preferences, risk perception, and information exchange at the time of the treatment decision. Survey reports were linked to claims data and laboratory results for a diverse sample of privately insured women who had all received the genomic test. The methodology includes multivariate logistic regression models, a test for mediation using the Karlson-Holm-Breen method for nested logistic models, and a test for moderation using the inclusion of an interaction term. Limitations of the studies include a retrospective design, lack of information on the physician perspective, and omitted clinical factors that may confound the results.

Results support that 1) risk perception mediates the effect of patient preferences on the treatment decision and is a suppressor of this effect, 2) information exchange moderates the effect of risk perception on the treatment decision, and 3) those relationships explain in part variations in treatment decisions observed in this sample. Specifically, we found variations in decision by race/ethnicity consistent with significant variations in risk perception and information exchange by race/ethnicity.

The dissertation provides new knowledge on patient factors influencing the treatment decision. Importantly, those factors are mutable and suitable targets for interventions. Those factors may also be relevant to address disparities in breast cancer care, as they are strongly associated with race and ethnicity.

The dissertation of Catherine Claire Chanfreau is approved.

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University of California, Los Angeles

2015

To Guillaume, Antoine, and Jeremy

Thank you for your love and support in this new adventure!

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LISTS OF ACRONYMS

ASCO	American Society of Clinical Oncology
CBSA	Census Core Based Statistical Area
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
ER+ LN–	Estrogen receptor (i.e., hormonal receptor) positive, Lymph Node negative
ER	Estrogen receptor
FDA	Food and Drug Administration
HMO	Health Maintenance Organization
KHB	Karlson-Holm-Breen method for nested nonlinear probability models
LN	Lymph Node
NCCN	National Comprehensive Cancer Network
NASBP	National Surgical Adjuvant Breast and Bowel Project
PPO	Preferred Provider Organization
RS	Recurrence Score
SD	Standard Deviation
SES	Socioeconomic Status
US	United States
ZIP	Zone Improvement Plan

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SELECTED PEER-REVIEWED PUBLICATIONS IN BIOMEDICAL RESEARCH

(Selected out of 30 publications; †: Corresponding Author; *: Co-First Author)

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

The development of personalized medicine has the potential to greatly improve the quality of care by better tailoring the treatments to the individual characteristics of the patients. But it may require efforts from both physicians and patients to share the decision-making. Physicians may have limited amount of time during the visit to explain in details the risks and benefits of different treatment options. Also, patients may find it challenging to balance those risks and benefits using probabilistic outcomes. The situation may be complicated if patient preferences and attitudes are in conflict with the recommendation coming from individualized test results. In this context it is important to define the patient-related factors and physician-related factors that may intervene in treatment decisions, and which of those factors may constitute suitable targets for interventions that aim to facilitate the process. Personalized medicine is already at work in oncology practices for breast cancer care, with the use of genomic tests that predict the risk of tumor recurrence and guide treatment for individual patients. Those genomic tests provide a model for the studies in the dissertation.

The research aims to expand on existing conceptual frameworks modeling the effect of patient-related factors and physician-related factors in the context of a medical decision regarding the choice between treatment options. A second objective is to define mutable factors that may help improve decision-making. Finally, to test hypotheses based on the model, we examined patient factors that may influence the treatment decision, and we focused on race and ethnicity that may shape patient attitudes and preferences.

The three papers of the dissertation use data from a national survey of privately insured women who received the genomic test to guide the decision of adding chemotherapy during their breast cancer treatment. The survey data offers rich documentation of the patient perspective on

treatment and decision process in a diverse, non-elderly population, and was augmented by linkage to individual claims and laboratory results. The first paper shows that risk perception intervenes on the relationship between patient preferences and treatment decision. The second paper shows the significant interaction of risk perception and information exchange on the treatment decision. Finally, based on the significant variations in risk perception and in information by race and ethnicity, the third paper examines the association of race, ethnicity, and other patient factors with variations in the treatment decision. Identifying risk perception and information exchange as factors that may impact the treatment decision is important as both are mutable and constitute suitable targets for interventions.

This first chapter provides an introduction on personalized medicine and its application in breast oncology to guide treatment decisions, a conceptual framework used to identify factors intervening in decision-making, an overview of the approach, and the new contributions of the research.

1.2 BACKGROUND

1.2.1 Personalized Medicine: Difficult Translation into Practice

Personalized medicine holds the promise of improving the quality of health care by tailoring treatments to the needs of individual patients (Kalia, 2013). Also called "precision medicine", it uses patient-specific information to predict individual patterns of disease and optimize treatment decisions (Institute of Medicine, 2012; National Research Council, 2011). Despite the rapid proliferation of genetic and genomic tests, their translation into clinical care has been slow, in part due to the limited body of evidence for their clinical utility (Bombard et al., 2013; Burke and Korngiebel, 2015; Phillips et al., 2013). The biggest field of applications for personalized medicine so far is cancer care. The past ten years have been marked with the translation from bench to bedside of genomic tests that guide medical decisions by providing objective measures for the desirability of a treatment at the tumor level. This information may also facilitate the sharing of decision between physicians and patients, in particular by balancing individual risks and benefits of treatment options.

Although it is widely expected that personalized medicine will improve health outcomes, it is quite possible that it will also increase health care disparities (McClellan et al., 2013). These new technologies are costly, and their diffusion may be slower in medical centers with lower resources that are more likely to care for underserved populations (Coughlin et al., 2008; Link et al., 1998). Beyond the issue of access and cost, genomic tests may also worsen disparities by giving more importance to patient-physician interaction and patient involvement in decision-making. Low levels in education and health literacy may penalize patients when it comes to interpreting risk and understanding probabilities inherent to personalized medicine (Davis et al., 2002). Cultural discordance and language barriers may further complicate the task if physicians

feel insufficiently trained in how to communicate about those new technologies (Allford et al., 2013). Patients may feel confused if the test recommends a treatment in conflict with their preferences or expectations. So, more information is needed to understand decision-making in the context of genomic testing and how it may vary with patient preferences (Burke and Korngiebel, 2015; Center for Medicare and Medicaid Services, 2015; Chang et al., 2014; Kalia, 2013; Kohli-Laven et al., 2011; Peabody et al., 2014; Polacek et al., 2007).

1.2.2 Improving Breast Cancer Care Through Individualized Treatment

Personalized medicine is already at work in breast cancer treatment. Since 1990, progress in treatment and early detection have significantly improved prognosis. While breast cancer remains the second cause of cancer-related deaths for women in the U.S., mortality has steadily declined, and 5-year survival has increased from 63% in the 1960s to 90% today, reaching even 99% survival for early-stage localized breast cancer (American Cancer Society, 2012). A major area of progress was the identification of biomarkers (such as the estrogen receptor) that are predictors of outcomes and indicators for targeted therapies. Treatment for hormone receptor-positive tumors, or hormonal therapy, includes the drugs tamoxifen and aromatase inhibitors that block the hormonal pathway feeding the growth of tumor cells (Puhalla et al., 2012). Over the years, large prospective studies have demonstrated the effectiveness of hormonal therapy and chemotherapy for the treatment of estrogen receptor–positive, lymph node–negative (ER+ LN-) breast cancer; they also provided evidence that the added benefits of chemotherapy may not exceed the toll of its toxicity for patients at lower risk of recurrence (Fisher et al., 1989; Fisher et al., 1997; Fisher et al., 2004). These observations have led to the development of genomic tests predicting recurrence risk at the individual tumor level, based on the rationale that identifying patients at lower risk of recurrence should improve quality of care and quality of life by avoiding

overtreatment with chemotherapy (Paik et al., 2004; Paik et al., 2006; van de Vijver et al., 2002). Genomic tests determine the level of expression for a precise set of genes, (or gene-expression profile) on the tumor tissue collected during surgery. Following quantification, a proprietary algorithm uses the data to evaluate the risk of cancer recurrence (Paik et al., 2004; Paik et al., 2006). As a complement to traditional clinical pathology that examines the morphology of the tumor cells, genomic tests may help in identifying patients who are at low risk despite a poor differentiation of the tumor cells, or a larger tumor size (usually, signs of poor prognosis); and patients who are at high risk despite a well-to-moderately differentiated tumor, or a small tumor size (Paik et al., 2004).

The addition of genomic testing in the care of early-stage ER+ LN- breast cancer has marked an important change in practice, with the revision of guidelines from the American Society of Clinical Oncology (ASCO) and from the National Comprehensive Cancer Network (NCCN), which previously recommended adjuvant chemotherapy for all breast cancer patients (Harris et al., 2007; NCCN, 2008).

1.2.3 The Natural History of Oncotype DX

Currently, the genomic test most widely available in the U.S. is Onco*type* DX® from Genomic Health Int. (Redwood City, CA). In 2013, more than 100,000 women were newly diagnosed with early-stage breast cancer, and about 60% of them were tested with Onco*type* DX (Genomic Health, 2013). Onco*type* DX produces a Recurrence Score (RS) based on the expression of 16 genes involved in cell proliferation, tumor invasiveness, and hormonal response, mechanisms that are predictive for the response to chemotherapy and the probability of cancer recurrence (Paik et al., 2004). The numeric score on a scale of 0–100 is converted into three risk categories

using precise cutoffs: low risk for RS < 18 (mean 10-year recurrence rate, 6.8 percent); intermediate risk for RS, at 18–30; and high risk for RS >30 (mean 10-year rate of recurrence, 30.5 percent; Paik et al., 2004). In this framework, patients at high risk should receive adjuvant therapy in addition to hormonal therapy, whereas patients at low risk are prescribed hormonal therapy alone. The benefit of chemotherapy is uncertain for patients at intermediate risk, and evaluation is still ongoing to determine the best practices in the setting of the TAILORx trial (Sparano, 2006). Until then, guidelines recommend the combination of chemotherapy and hormonal therapy for patients at intermediate risk while incorporating patient preferences (NCCN, 2008).

The development of Onco*type* DX is a unique example of test designed for a rapid integration in the practice setting (Kohli-Laven et al., 2011). The assay was developed to use the material most commonly available after surgery (i.e., formaldehyde-fixed paraffin-embedded tissue blocks used in all pathology laboratories; Kohli-Laven et al., 2011; Paik et al., 2004). The development and validation of the algorithm calculating the RS took advantage of a large databank of tumor tissues collected during the NASBP clinical trials that compared the efficacy of a combination of chemotherapy and hormonal therapy to hormonal therapy alone (Paik et al., 2004). As a laboratory-developed test, the reliability and accuracy of Onco*type* DX were assessed under the regulation defined by the Clinical Laboratory Improvement Amendment (CLIA; a process distinct from the FDA regulations that apply to drugs and devices; Kohli-Laven et al., 2011). Following its introduction in the U.S. in 2004, Onco*type* DX was validated prospectively in the U.S. and abroad (Habel et al., 2006; Lyman and Kuderer, 2006; McVeigh et al., 2014). After obtaining support from the NCCN Task Force in 2006, the genomic test was

rapidly incorporated in professional guidelines emitted by ASCO in 2007, and by NCCN in 2008 (Harris et al., 2007; NCCN, 2008).

Two large studies documenting the ordering of Onco*type* DX in the U.S. in 2009 found that only a small fraction of the eligible patients received the test, ranging from only 10% in the Medicare population (Dinan et al., 2015), to 30% among patients aged 45 years and more treated in The US Oncology Network (Chen et al., 2013). In both studies, the test use was found greatest among patients with ER+LN–, invasive tumor larger than 1 cm, as recommended by the NCCN guidelines (Chen et al., 2013; Dinan et al., 2015). More recently, a report by Genomic Health estimated that 60% of all eligible patients received testing in the U.S. in 2013 (Genomic Health, 2013). Currently, about 95% of the payers offer coverage for Onco*type* DX for early-stage ER+LN– breast cancer (Deverka et al., 2012), including most private payers, Medicare, and Medicaid in 35 states (Genomic Health, 2014).

For several years Genomic Health has held a *de facto* monopoly on genomic testing for breast cancer in the U.S. as Onco*type* DX was the only genomic test for breast cancer performed on fixed tissues. The situation is likely to change with the emergence of competitor tests in 2012-2013. In 2012 Agendia Inc. (Irvine, CA) expanded the applications of the MammaPrint® test from frozen tissues to fixed tissues resulting in a rapid diffusion in the U.S. (Ray, 2012). In late 2013, a third test was introduced, Prosigna by NanoString Technologies, Inc. (Seattle, WA). It is still too early to predict how the market will evolve, as the three tests use different systems, and result in different classifications of the patients, but concurrence may drive down the price of Onco*type* DX (currently, about U.S. $4,000-4,500).

1.2.4 Benefits of Genomic Tests in Informing Chemotherapy Decisions

Many benefits are expected from the use of genomic tests: improving the care for patients at high risk of recurrence that standard pathology may have not identified; improving the quality of life for women at low risk able to avoid chemotherapy; providing patients with an objective risk measure that may help in treatment decisions (Defrank et al., 2013a); and increasing quality of care while achieving cost-effectiveness (Klang et al., 2010; Tsoi et al., 2010). For low-risk patients, the benefits of avoiding chemotherapy are likely to persist long after the course of the treatment, as chemotherapy is associated with long-term adverse effects on health (Ganz et al., 2002; Ganz et al., 1998). Genomic tests may also be of particular value for younger patients. While patients aged less than 50 years represent only 25 % of the new cases of breast cancer, they are also more likely to develop aggressive tumors, with chemotherapy resulting in greatest gains in survival (Ganz et al., 2003). However, the consequences of chemotherapy in this population that include early menopause and threats to fertility, may contribute to poorer quality of life (Ganz, 2005; Ganz et al., 2003). For these younger patients, the result of the genomic test may help achieve a better evaluation of risks and benefits of adding chemotherapy, and improve long-term survivorship. It may also comfort patients at high risk in their decision to receive chemotherapy.

Several studies have shown that the use of genomic tests in practice is indeed associated with an overall decrease in the use of adjuvant chemotherapy (Chen et al., 2013; Haas et al., 2011a; Hassett et al., 2012; Lyman and Kuderer, 2006; Partin and Mamounas, 2011). Genomic test results were found to change the initial treatment decision for 25-44% of the patients tested (Ademuyiwa et al., 2011; Asad et al., 2008; Henry et al., 2009; Holt et al., 2013; Lo et al., 2010; Rayhanabad et al., 2008). The change in decision is predominantly for low-risk patients avoiding

chemotherapy that was initially planned. In addition, a small number of patients who were initially recommended hormonal therapy alone are identified at intermediate-to-high risk by the genomic test, leading to the initiation of chemotherapy (Ademuyiwa et al., 2011; Asad et al., 2008; Henry et al., 2009; Holt et al., 2013; Lo et al., 2010; Rayhanabad et al., 2008). Those results support the value of the test for breast cancer management, but evidence has also emerged that disparities exist in the ordering of the test and that genomic tests were offered less frequently to minority women compared to White women (Haas et al., 2011b; Hassett et al., 2012; Lund et al., 2012). A differential ordering of the test may add to existing sources of disparities in breast cancer treatment, and compromise gains in quality of care for minority women.

1.3 CONCEPTUAL FRAMEWORK

To model the role of patient factors in treatment decisions, we used the guidance of existing theoretical frameworks modeling health-related decisions: the Health Behavior Framework (Bastani et al., 2010), the Shared Decision Making framework (Charles et al., 1997), and the Framework for Patient-Centered Communication in Cancer Care (Epstein and Street, 2007). Those frameworks model the effect of patient characteristics and provider characteristics on health behaviors, and help guide the analysis of the role of communication in the treatment decision. We aimed to expand on those frameworks with the addition of pathways that intervene on the relationship between patient characteristics and treatment decision.

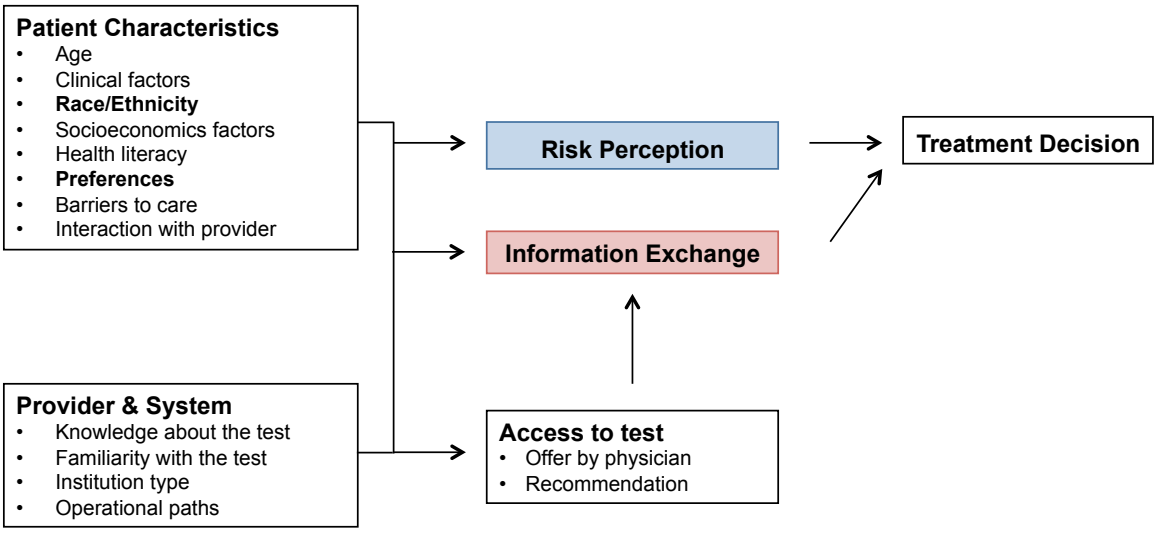


Figure 1.1: Conceptual framework and factors that may influence the treatment decision.

Patient characteristics include race/ethnicity, age, and socioeconomic status (SES) that are known to impact breast cancer care (Bastani et al., 2010; Epstein and Street, 2007). The model also includes health literacy that has been associated with differences in understanding the result of a genomic test (Tzeng et al., 2010), and together with education, may strongly influence the perception of recurrence risk (Defrank et al., 2013a; Donelle et al., 2008; Lillie et al., 2007; O'Connor et al., 1987). Those characteristics are also relevant to health disparities, because of their strong associations with race/ethnicity in the setting of cancer care, such as younger age at diagnosis, lower SES, and lower health literacy. Patient characteristics may also influence the perception of chemotherapy value for their treatment, and anticipated adverse effects on quality of life and body image may weigh significantly in the decision of accepting chemotherapy (Masi and Gehlert, 2009; Yellen et al., 1994). The importance of these elements in decision-making might vary depending on education and cultural values.

We also incorporated factors that may be influential in treatment decisions: family support, opportunity cost of time, and influence of the work status (Bastani et al., 2010). Family composition (marital status, household size, children age), family involvement in the medical care, and social activities outside of the medical setting may provide measures for social support, with the hypothesis that lower level of social support might be perceived as a barrier to a more strenuous therapy. Having younger children may also lead women to decline chemotherapy if the recurrence risk is not high, due to the impact of the treatment on daily activities. In contrast, if a woman perceives a high risk, she may be willing to accept a treatment even if the benefits are small compared to the potential harm (Duric et al., 2008). Social support may also have a positive impact during the medical encounter, as the presence of family members and other companions may help promote patient advocacy and improve information retention (Harder et al., 2013). Opportunity cost of time (or the time dedicated to treatment and that could have been used for other activities) is another important factor in the decision: time includes not only the sessions of chemotherapy, but also time for transportation, and side effects and fatigue that may be barriers for other activities. It is worth noting here that the effects of receiving chemotherapy are not limited only to the course of the treatment, as there may be long-term adverse effects on health, including fatigue, insomnia, and poorer functioning (Ganz, 2008; Ganz et al., 2002; Rey et al., 2012). The impact of opportunity cost of time may be particularly important for younger, insured population, as private insurance is most often tied to employment of the patient or her spouse.

Finally, we included elements of the patient-physician interaction as perceived by the patient (quality of communication and physician mistrust); patient-physician interaction is important in the model, as it is likely to influence the degree of collaboration between patient and physician in

decision-making (Epstein and Street, 2007). Provider mistrust is a significant issue for minority patients that may impact quality of care and patient satisfaction with the treatment decisions even if they are appropriate decisions (Doescher et al., 2000; Waters et al., 2010). Among African Americans, physician mistrust has been found to relate to mistrust towards the medical system in general and genetic testing in particular (Kolor et al., 2012).

Based on existing frameworks and the literature (Blank et al., 2006; Epstein and Street, 2007; Politi et al., 2012), our model for treatment decision includes two intervening paths relevant to intervention design. Those paths featured actionable elements suitable for interventions to improve the use of the genomic test in decision-making. A first path involves the indirect effect of patient preferences for chemotherapy through risk perception, as elaborated in Chapter 2. The second path described in Chapter 3, incorporates patient characteristics and elements of the patient-physician interaction into information exchange. We proposed that the quality of information exchange influences the treatment decision, and we examined the role of risk perception as a moderator of the relationship between information and treatment decision. Finally, based on the strong association of race/ethnicity with both risk perception and information exchange, Chapter 4 examines the effect of race/ethnicity itself on the treatment decision. More specifically it focuses on the women at low and intermediate risk of recurrence for whom the treatment decision may be more strongly associated with preferences and non-clinical characteristics than for patients at high risk.

1.4 OVERVIEW OF THE APPROACH

1.4.1 Research Questions

The objective of this study is to expand on existing frameworks that model the process of decision-making in a medical setting, and to identify factors influencing treatment decision in the context of a genomic test. We focused on mutable factors that may constitute suitable targets for interventions aiming to improve the quality of care and to prevent disparities in breast cancer treatment. The studies tested the following hypotheses regrouped into three research questions.

QUESTION 1: Patient Preferences, Risk Perception and Treatment Decision

Hypothesis 1a: Lower preference for chemotherapy is associated with lower level of risk perception regarding the tumor recurrence.

Hypothesis 1b: Higher perception of risk is associated with higher use of chemotherapy.

Hypothesis 1c: Risk perception suppresses the effect of patient preferences on the treatment.

This research question is analyzed in Chapter 2.

QUESTION 2: Interaction of Information Exchange and Risk Perception on the Treatment Decision

Hypothesis 2a: Variations in information exchange between patient and physician are associated with race/ethnicity.

Hypothesis 2b: Both information exchange and risk perception are significantly associated with the treatment decision.

Hypothesis 2c: There is a significant interaction of the effect of information exchange and the effect of risk perception on the treatment decision.

This research question is analyzed in Chapter 3.

QUESTION 3: Racial Variations In Treatment Decision Following Genomic Testing for Recurrence Risk

Our model predicts that patients who perceive lower level of risk but lack knowledge about the test result are likely to have increased odds of receiving chemotherapy, whereas lacking the knowledge about the test result may suppress the effect of elevated risk perception. Both African-American patients and Hispanic patients were at increased odds of not knowing their test result, but Hispanic women were also more likely to perceive higher risk of recurrence than White women, leading to the hypotheses analyzed in Chapter 4:

Hypothesis 3a: African American patients are more likely to receive chemotherapy than White patients after controlling for recurrence score, age, and other factors.

Hypothesis 3b: Due to the counteracting effect of lower risk perception and lower information exchange, variations in treatment decisions are less pronounced for Hispanic women than for Black women, after controlling for recurrence score, age, and other factors.

1.4.2 Data Source

This retrospective study combines data from a patient survey linked to claims information from the third largest national health insurance provider, Aetna (Hartford, CT), and laboratory records provided by Genomic Health, Inc. (Redwood City, CA).

1.4.3 Population

Eligible participants were women younger than 65 years, who had received a claim for the genomic test Onco*type* DX between January 2009 and November 2012. Clinical eligibility (recent diagnosis of ER+ LN- breast cancer, with tumor size < 1 cm in diameter for Her2-positive tumor) was established prior to testing through pre-authorization by the health plan.

Eligibility criteria also included patient's continuous enrollment for at least 3 months before the test, and six months after to ensure completion of chemotherapy, and no prior history of cancer based on the health plan records.

Based on 2009 claims, 20% of the eligible women were expected to be of minority groups, so those groups were oversampled using information from the health plan, as described in the Appendix. Briefly, when information was not available, race/ethnicity was estimated using the Bayesian Improved Surname Geocoding (BISG) method that combines last name and geocoding analysis (Elliott et al., 2008). All eligible women identified as non-White (n=705) were invited to take the survey, and a random sample among the women identified as White was matched in proportion according to age categories (<50 and >= 50 years old), geography, and diagnosis year. Assuming a conservative response rate of 40%, our power analysis estimated that a sample size of 300 White and 300 non-White participants would result in 90% statistical power.

The study protocol was approved by the Office of the Human Research Protection Program, at UCLA.

1.4.4 Data Collection

The survey strategy is detailed in the Appendix. Briefly, a mailed survey was administered between August 2nd, 2013 and December 31st, 2013. The questionnaire explored patients' perspective on their medical treatment, the use of the genomic test, the quality of the interaction with their physician, and the factors that had influenced the decision about chemotherapy. It also collected self-reported race/ethnicity and demographic information.

Survey data were linked to health plan information for individual respondents: age at the time of the test, indication of comorbidities, health plan type, and geographic information (ZIP codes recoded into 2011 U.S. Census regions, and Core Based Statistical Areas), as well as

confirmatory information about year of testing, and use of chemotherapy, radiation, and surgery. The dataset was complemented by laboratory results, including the actual risk score on a scale of 0–100, confirmatory clinical information (ER, PR and Her2 status), and geographic information for the physician ordering the test (city and state).

Non-response bias was tested by comparing aggregated information obtained from the health plan on the groups of respondents and non-respondents, including age distribution, year of testing, U.S. Census region, health plan type, and minority status used in the sampling.

1.4.5 Survey sample

4,410 eligible patients were identified among 6,650 members receiving a claim for a recurrence risk test between January 2009 and November 2012 (Appendix, Figure A1). All 728 members identified as non-White were included, and 728 women were randomly selected among the 3,682 members identified as White, after stratification by year of diagnosis, age (<50 years, and 50–64), population density (rural/urban/suburban), and U.S. Census region to balance the groups. 24 potential participants were further excluded for receiving a recurrence test other than Onco*type* DX, and 8 because of an invalid mailing address, resulting in 1424 survey invitations. The survey was launched on August 2nd 2013, and closed on December 31st 2013. Target goals were exceeded with a total of 896 responses and a high response rate of 63%. As anticipated, the response rate was higher for White than non-White women (77% versus 48%). Online responses represented only 8% of all responses.

Demographic characteristics of respondents and non-respondents were compared to assess if there was a nonresponse bias (Appendix, Table A1). Respondents tended to be slightly older, more frequently White, and had more often reported on their race/ethnicity to the health plan, compared to non-respondents (all, $P < .05$). No differences in distribution were found between

the two groups by year of test claims, or by type of health plan (POS, HMO, or PPO); in contrast, significant geographic variations were identified, with respondents living more frequently in the North Central and West regions, and non-respondents living more frequently in the South region.

Self-report on race/ethnicity in the survey (available for 890 respondents out of 896) was compared to the information used in sampling to assess misclassification. Only 9% of the non-White respondents were misclassified as White, and the rate was higher for White (20%). Misclassification rates resulting from indirect estimation were similar to those reported in a validation study performed on a similar insured population (Elliott et al., 2009).

1.4.6 Geographic distribution of the patients

Respondents resided in 176 CBSA (Core-Based Statistical Areas, U.S. Census 2010, equivalent to metropolitan areas of 10,000+ inhabitants) in 45 states. Clusters of patients by CBSA tended to be small, on average 4.6 participants (SD 8.0), and only 25 areas regrouped more than 10 participants (Appendix, Figure A2). While the participants more frequently resided in the West and Northeast regions, the areas most represented at the CBSA level were New York, NY (n=57); Houston, TX (n=55); Atlanta, GA (n=52); Philadelphia, PA (n=44); and Washington, DC (n=38), with these four CBSA accounting for 27% of the sample. A similar pattern was observed for clustering of the patients by site providing care (Appendix, Figure A3).

1.5 LIMITATIONS

An important limitation of the study is the retrospective design, as patients were surveyed after the treatment completion. Treatment experience may have tainted the answers to questions probing the state of mind of the patient at the time of the decision, and the survey measures for

risk perception and patient preferences may be different than if the questions had been asked shortly before the treatment decision. In addition, the sampling frame required a large window of time (2009-2012) to identify a sufficient number of eligible participants. The recall time (up to 4 years) may have affected the accuracy of patient reports, and it is possible that patients reported lacking information that was in fact communicated and then forgotten. The effect of time was in part controlled for using indicators for the year of treatment. The validity of the patient reports was in part supported by the high agreement with claims data regarding some of the medical procedures, but it is likely that the recall for strenuous treatment such as chemotherapy would be higher than for the result of a diagnostic test.

Omitted variables are another important limitation of the study. First, we lack information from medical records that would indicate tumor stage (I or II), tumor grade, and tumor size that are important clinical factors for the treatment decision. Information on family history of cancer is also missing, which might influence both the patient risk perception and the treatment decision. Finally, medical records may bring information on discussions about test results that may have occurred between physician and patients.

Second, the dataset provided detailed information on the patient perspective, but the information on providers is very limited and granular. Only names and cities for ordering providers were collected from the laboratory, and the mix of providers was not limited to oncologists but also included pathologists. Also, few providers were linked to more than one patient in the dataset, and only 10 sites (identified by city and state) regrouped more than 10 patients. This is an important limitation for several reasons. It is likely that communicating about the test result may be easier for providers who are more familiar with the test because they are

using it more often, or have used it for a longer time. As the patients were treated as early as 2009, it is possible that the diffusion of the technology was still going on at that time, and it may have been still relatively novel for some providers. Those issues are in part addressed using the indicators for the year of treatment. Also, we are missing important information on the institutions such as the type of organization (e.g., academic center, community center, specialized cancer center, or private practice) that may impact the pathways of care and the role of the genomic test result in the treatment decision.

Another limitation of the study is the nature of the sample that may introduce both a selection bias and a response bias at the level of the patient population.

Regarding the selection bias, the study is capturing only the perspective of women for whom the genomic test was ordered. The study is missing the perspective of women to whom the test was not offered, and patients who may have desired to be tested, but could not because of cost or ineligibility. Another selection bias may result from the characteristics of this privately insured sample with overall high levels of SES and health literacy. In particular, minority women in the sample tended to have high education level and high income, and most were working full-time, so they may not constitute "typical" minority patients. Also, the survey was limited to members receiving communication from their health plan in English, and provided only in English. However, it could be argued that if disparities are detected in this population, it is very likely that the situation may be worse in other patient populations. Finally, all women surveyed are members of a single health plan, which may constraint the geographic distribution of the sample to the markets covered by this insurer, and therefore not be representative of the national patient population receiving the test.

Nonresponse bias was partially assessed by comparing the demographic characteristics of respondents and non-respondents using aggregated data from the health plan. Respondents tended to be slightly older, and more frequently White, compared to non-respondents. However, no information was available on the diagnosis, medical treatment, and current health status for the non-respondents. We cannot exclude that non-respondents included patients who were disabled with metastatic disease. Patients who received chemotherapy, or were at a high-risk recurrence score may have been more likely to be non-respondents. Those two factors may have led to a refusal to respond if the survey reminded a patient of a painful experience, or reignited feeling of decisional conflict or uncertainty about her prognosis. Some women may also have found the survey non relevant.

1.6 STRENGTHS

Despite these limitations, the research has several important strengths.

First, the research participates in developing methods that will help evaluate the utility of personalized medicine in the real-world setting. The measures used in the studies may be imperfect due to the retrospective design, but they bring information on relationships between patient preferences, risk perception and information exchange related to an actual treatment decision rather than hypothetical treatment choices. The research also identifies these concepts as important to measure in the context of a treatment decision based on genomic test. By using measures for those concepts that are already validated in the literature on cancer care decision, this research work demonstrates that it may possible to rapidly develop methodologies for the field of personalized medicine by following the example of similar fields.

Second, this study is the first study that examines patient perspective on the use of a genomic test in the real world using a diverse, national sample. The combination of patient reports, claims

data and laboratory results offers a detailed documentation of the process, and helps identify elements of the decision process that vary by race and ethnicity, and other patient characteristics, such as a young age, and opportunity cost of time.

Finally, the research aims to produce knowledge that can be rapidly applied in practice. It points to mutable factors that can be the targets for interventions supporting physician and patient in collaborating in treatment decisions. In particular, we identified variations in risk perception and information exchange by race and ethnicity that may help tailor interventions to the needs of different racial/ethnic groups.

1.7 INNOVATIONS OF THE RESEARCH

The dissertation aims to expand on existing frameworks and help define pathways intervening in decision-making using a genomic test. In particular, it brings new knowledge on the relationships between patient characteristics, risk perception, and information exchange in the context of a treatment decision. In this study we focused on race and ethnicity that are strongly associated with patient attitudes and preferences, but may also play an important role in the quality of the interaction between patient and physician. But the approach and methods used here may easily be transposed to the study of other relevant patient characteristics.

An important innovation of the dissertation is the finding that risk perception intervenes on the relationship between patient preferences and treatment decision. The results support that patient preferences for chemotherapy influence the treatment decision through the filter of risk perception, and the full effect of the preferences is revealed after controlling for risk perception in the model for the treatment decision. Based on the literature risk perception is a mutable factor that may be changed by patient education (Epstein and Street, 2007). Therefore, the result supports the need for patient-centered interventions that may lead to a more informed decision

through education on the risks and benefits of treatment options. Beyond the treatment decision itself, helping women understand their risk of recurrence more accurately may help in supporting adherence to protective behaviors that may prevent recurrence, an identified cause of disparities among long-term breast cancer survivors (White et al., 2013).

A second innovation of the research is to show that differences in information exchange may relate to differences in treatment decision by race/ethnicity. Furthermore, the finding of a significant interaction between risk perception and information exchange suggests that interventions targeting providers are needed. Those interventions should promote physician awareness about differences in risk perception by race and ethnicity, and support physicians in engaging in an effective information exchange with patients of different backgrounds. Increasing physician awareness on patient characteristics and attitudes that may influence the decision-making is likely to improve shared decision-making.

Third, the research fills a gap in the knowledge about the use of new technologies in breast cancer care in a diverse population: previous studies have often had poor representation of minority groups, or a limited geographic representation. Here we used data from a large sample with sufficient power to look at racial/ethnic groups separately. Also, the study focused on younger women, often part of the workforce, and whose preferences may be markedly different from the older population usually studied. An important finding is that quality of care does not imply equity: while the overall quality of care was excellent, important disparities in knowledge were observed that may impact patient satisfaction with the care received, and long-term outcomes of the treatment

Finally, our model may be adapted to other medical decisions where uncertainty exists regarding the choice between different treatment options. It may more generally help in

understanding the role of the patient-physician interaction in decision-making. This is an important issue for patient-centered care in general: as patients are expected to be more responsible for their care, we need to better understand the factors that influence this process to help patients achieve informed decisions.

CHAPTER 2

PATIENT PREFERENCES, RISK PERCEPTION AND TREATMENT DECISION

2.1 ABSTRACT

Purpose

Willingness to undergo treatment may vary with risk perception and patient preferences, and differences in risk perception and preferences between patients and providers may result in decisional conflict and poorer adherence to treatment.

Patients and methods

We used a retrospective study design and multivariate analyses to examine chemotherapy preferences and risk perception in a national sample of privately insured women aged less than 65 receiving genomic testing for early-stage breast cancer in 2009–2012. Responses to a mailed survey with oversampling of non-White patients were linked to claims data and laboratory results. We examined the association of patient characteristics with variations in preferences and risk perception, and the effect of those factors on the treatment decision to receive chemotherapy. Logistic regression models were adjusted for patient demographics, clinical characteristics, and factors that may influence the decision to undergo treatment. We tested for the indirect effect of chemotherapy preference on treatment decision via risk perception using the Karlson-Holm-Breen method.

Results

Patient preferences for chemotherapy varied significantly with age, race/ethnicity, socioeconomic status and health literacy. Risk perception was significantly associated with age, recurrence risk predicted by the genomic test, and low preference for chemotherapy. Furthermore, we found that risk perception suppresses the effect of patient preferences on the treatment decision.

Conclusion

Variations in patient preferences and risk perception may influence the treatment decision when there is uncertainty about the best treatment options. Both patient preferences and risk perception are mutable characteristics that may constitute targets for interventions to improve shared decision-making.

2.2 BACKGROUND

Each year about 100,000 women are diagnosed with early-stage breast cancer in the U.S., and about 60% of them receive the Oncotype DX genomic test to help guide the choice between treatment options based on their individual risk of tumor recurrence (Genomic Health, 2013).

Use of the Recurrence Score in Treatment Decisions

The genomic test produces an individual recurrence score (RS) that predicts both the risk of tumor recurrence and the additional gain in preventing recurrence from combining hormonal therapy with adjuvant chemotherapy (Paik et al., 2004; Paik et al., 2006). Current professional guidelines recommend the use of the genomic test for estrogen receptor-positive, lymph node-negative breast cancer to identify women at low risk of recurrence (RS <18) who may safely avoid chemotherapy and its adverse effects (Harris et al., 2007; NCCN, 2008). The test also helps detect women for whom a high risk of recurrence (RS >30) was not established based on traditional prognostic criteria, and for whom guidelines recommend chemotherapy. Uncertainty remains on what constitutes the best treatment option for patients scoring at RS 18–30, and a clinical trial is currently underway that may answer whether or not intermediate-risk patients benefit from the additional of chemotherapy to hormonal therapy (Sparano, 2006). While current guidelines recommend chemotherapy for intermediate-risk patients, they also recommend the consideration of patient preferences in the treatment decision towards therapeutic options (NCCN, 2008).

The genomic test provides a laboratory-based score for the 10-year risk of cancer recurrence, but this information may be difficult to understand for some patients (Brewer et al., 2009b; O'Neill et al., 2007) To facilitate communication, the continuous score is classified into

three risk categories, but the underlying score is a continuous function of the likelihood of recurrence. Accordingly, patient with scores RS =17 and RS =18 are classified into low and intermediate risks, respectively, but the absolute difference in recurrence rate at 10 years between the two scores is actually small (about one-percentage point; Paik et al., 2004). Depending on their risk perception, patients with a score close to the boundary between the two adjacent risk categories may have difficulties balancing the risk and benefits of the two treatment options (hormonal therapy alone, or combined with chemotherapy).

Risk Perception as a Mediator of the Treatment Decision

The influence of risk perception on patient willingness to receive chemotherapy treatment has been documented in studies using hypothetical scenarios about test results (Brewer et al., 2009a; Defrank et al., 2013a). In those studies, when results from genomic tests and standard clinical indicators were conflicting, women tended to assign more weight to the result from the genomic tests (Brewer et al., 2009a; Defrank et al., 2013a). DeFrank and colleagues (2013a) proposed that the impact of the test result on the treatment decision was mediated by risk perception. Those results contrast with studies looking at the impact of other objective measures of risk and risk predictors. For instance, patient risk perception did not coincide with the Gail score predicting breast cancer risk, or with the knowledge that carrying a *BRCA1/2* mutation increases the risk of breast cancer (Brewster et al., 2007; Daly et al., 1996; Haas et al., 2005). Variations in risk perception were linked to differences in patient characteristics and preferences (Haas et al., 2005). In particular, women at increased risk of breast cancer were more likely to underestimate their risk of disease compared to women at average risk (Haas et al., 2005).

Risk Perception and Patient Preferences

An association between risk perception and patient preferences has now been well established. Patient preferences are traditionally measured using a time-tradeoff method (Brundage et al., 1998; Llewellyn-Thomas et al., 1996). Patients are asked to indicate the utility gain (e*.g.,* life years) that would make treatment, such as chemotherapy, worthwhile compared to the expected adverse effects using hypothetical scenarios. Studies eliciting patient preferences for breast cancer treatment have shown that patients may be willing to accept a treatment even if the benefit is very small, or if there is toxicity from the treatment (Duric et al., 2005; Hamelinck et al., 2014; Lindley et al., 1998; McQuellon et al., 1995). If her risk perception is high, a patient may be more inclined to accept treatment even if the benefits are uncertain (Duric et al., 2005; Hamelinck et al., 2014; Lindley et al., 1998; McQuellon et al., 1995). Most studies found wide variations between participants in how much survival time would make chemotherapy worthwhile, ranging from a 6-month gain being acceptable for most patients (Lindley et al., 1998) to a 1-day gain being sufficient for some patients (Duric et al., 2005). For example, the wide range of patient preferences is illustrated by a survey of women treated for early-stage breast cancer and asked about hypothetical treatment decisions for metastatic breast cancer. The study found that more than 90% of the respondents would accept chemotherapy for a 50% chance of gaining five years in life expectancy, whereas only 44% would accept chemotherapy for a gain of six months, and 12% would still accept it for a gain as little as one week (McQuellon et al., 1995). These important variations suggest a model where underlying patient characteristics influence risk perception that itself affects the decision.

Patient Characteristics as Predictors of the Treatment Decision Mediated by Risk Perception

The hypothesis for an indirect effect of patient characteristics on treatment decision through risk perception should be considered in the context of the Health Behavior Framework (Bastani et al., 2010), the Shared Decision Making framework (Charles et al., 1997), and Patient-Centered Communication in Cancer Care Model (Blank et al., 2006; Epstein and Street, 2007; Politi et al., 2012). These models provide guidance towards understanding the relationship of patient characteristics and communication with medical decisions, and highlight the importance of eliciting patient preferences (Blank et al., 2006; Epstein and Street, 2007; Politi et al., 2012). Including patient preferences in decision-making is important, as preferences may moderate the effect of communication on treatment decision (Epstein and Street, 2007). In particular, patients who identify a low level of preference for a treatment may be more receptive to information communicated by the physician about the different options than patients expressing strong preferences and whose opinion may not be changed with more information.

In the context of preference-sensitive decisions, incorporating patient preferences is likely to improve outcomes and to result in a decision more satisfactory for the patient (Politi et al., 2012). So, eliciting patient preferences may be most important for clinicians facing a patient who has not yet developed a strong preference for treatment choice (Politi et al., 2012). Eliciting patient preferences also allows clinician to verify patient preferences that do not always correlate with socio-demographic characteristics (Politi et al., 2012), and may conflict with physician preferences (Montgomery and Fahey, 2001; Slevin et al., 1990; Ubel et al., 2011). When explicitly identified, clinicians are less likely to misinterpret patient preferences. For instance, physician presumption that patients prefer to start chemotherapy without any delay was

identified as a potential barrier to the use of genomic tests with reports of chemotherapy being initiated before the test result was known (Weldon et al., 2012). As a result, variations in the weights put on patient preferences by providers may result in variations in treatment decisions.

Trade-off analyses between survival and toxicity of a hypothetical treatment have helped in identifying patient characteristics influencing preferences. For instance, patients who are younger, or at higher socioeconomic status, tend to favor survival while patients who are older, or at lower socioeconomic status, may prefer less toxicity or lower cost (Newcomb and Carbone, 1993; Wong et al., 2013; Yellen et al., 1994). Education is also influential, as well as health literacy and numeracy (Donelle et al., 2008; Lillie et al., 2007). A distinct concept from formal education, health literacy is the "ability to understand, engage and actively apply health information towards the goal of improving one's health." (Institute of Medicine, 2004). Health literacy has been shown to affect patient preferences and to influence the perception of recurrence risk. For instance, among post-treatment breast cancer patients asked to interpret the hypothetical result of a genomic test, women with low health literacy were found to be more likely to overestimate recurrence risk than women with higher health literacy; women with lower health literacy were also less sensitive to the difference between high and low risks when asked to make an hypothetical treatment decision (Brewer et al., 2009b). Health numeracy, a skill analogous to health literacy but applied to numeric and probabilistic information, is equally important, as low numeracy also results in a poor perception of risk and a greater sensitivity to extraneous factors (Reyna et al., 2009). Patient preferences were also shown to vary by race and ethnicity (Hawley et al., 2008; Phipps et al., 2003).

Several studies from Brewer and colleagues have documented the importance of health literacy for patients' understanding of the genomic test (Brewer et al., 2009b; Lillie et al., 2007;

Tzeng et al., 2010). In these studies health literacy was influential on using information from the test result in hypothetical decisions (Brewer et al., 2009b; Lillie et al., 2007; Tzeng et al., 2010). However, relatively little is known about how patient preferences may influence the actual utilization of genomic test results during the medical treatment. Here we examine the relationship between patient preferences, risk perception and treatment decision. In the context of this study, *patient preferences* is defined as the patient's willingness to undergo chemotherapy for a gain in additional life years; *risk perception* is the perceived risk of recurrence expressed by the patient; and the *treatment decision* is the decision made about whether or not the patient will receive chemotherapy in her breast cancer treatment. The finding of a significant effect of risk perception on the relationship between patient preferences and treatment decision would be relevant for intervention design as risk perception is a mutable factor sensitive to information (Epstein and Street, 2007).

We used data from a survey of privately insured patients who had completed their breast cancer treatment and had received the genomic test. We hypothesized that patient preferences were associated with differences in risk perception, and that in turn, risk perception was associated with differences in treatment decision. We predicted that the effect would be stronger among minority patients, who are at greater risk of lower health literacy and numeracy (LaVallie et al., 2012; Osborn et al., 2011). We took advantage of the detailed self-reported information on demographics and treatment experience to examine variations in risk perception relating to patient characteristics. Multivariate logistic regression models were adjusted for factors associated with risk perception (age, race/ethnicity, education, and health literacy), patient perception of the patient-physician interaction (quality of communication and physician

mistrust), and factors that may influence the treatment decision (family support, opportunity cost of time, and worry about work). We hypothesized that patient preferences were associated with risk perception, that differences in risk perception were associated with variations in treatment decision, and that risk perception was part of a mediation path between patient preferences and treatment decision.

2.3 METHODS

2.3.1 Data Source and Population

Data source, patient population, sampling frame and data collection are described in Chapter 1, Section 1.4. Briefly, this retrospective study used the responses from a mailed survey linked to claims data and laboratory records. Eligible women were privately insured, early-stage breast cancer patients younger than 65 years, who had received the genomic test Onco*type* DX between January 2009 and November 2012. The survey was administered between August 2, 2013 and December 31, 2013. The overall response rate was 63% with 896 respondents.

2.3.2 Measures

Patient preference for chemotherapy was measured using the hypothetical scenario, "Try and think back to the time you were considering chemotherapy for your breast cancer. Suppose that without chemotherapy you would live 10 years: how many more years of life would make 6 months of chemotherapy treatment worthwhile?" with response items: "2 years or less", "3 to 5 years", "6 to 10 years", "More than 10 years", or "No numbers of years would have been worthwhile." The values of the gains in years were modified to reflect a scenario of early-stage breast cancer (Mandelblatt et al., 2010; Ravdin et al., 1998). Choosing a gain less than 2 years

indicated a strong preference for chemotherapy, whereas choosing a gain greater than 10 years indicated a low preference. Refusing chemotherapy for any gain in time was interpreted as an aversion for chemotherapy. An indicator for reporting a *low preference for chemotherapy* was based on the choice of the item "More than 10 years" (vs. the other responses items); it was used as a proxy measure for unobserved patient characteristics, such as personal experience, health beliefs and cultural norms, that may result in low preference for chemotherapy.

Risk perception was measured by asking the participants about their personal perception of tumor recurrence risk: "When you were making decisions about your breast cancer treatment, what did you personally think the chance was that your breast cancer would come back in the next 10 years?" with response items: "Very low chance", "Low chance", "Moderate chance", "High chance", and "Very high chance." (Tzeng et al., 2010). The variable was recoded into 4 categories by pooling the reports of "High chance" and "Very high chance".

The *treatment decision* is the use of adjuvant chemotherapy during treatment (yes/no) determined by the existence of claims for the drugs most frequently used for breast cancer care based on a list established by an expert medical oncologist.

Patient Characteristics

Age at the time of the test was collected from claims data, and its squared value was added as a covariate in ordered logistic regression. Recurrence risk based on the genomic test was collected from the laboratory and coded into three risk categories (RS <18, low risk; RS = 18–30, intermediate risk; and RS >30, high risk). Self-reported race/ethnicity measured using the 1997 Office of Management and Budget (OMB) standards was reclassified into five mutually exclusive categories: Hispanic, Black, Asian, White, and Other (regrouping Native

Hawaiian/Pacific Islander, American Indian/Alaska Native, and multiracial with no preferred identification with one race). General health status ("excellent", "very good", "good", or "fair/poor"), educational attainment, and annual household income were collected in the survey. Demographic indicators based on the survey data included having an annual household income lower or equal to $40,000; having an education level of high school graduate or lower; having a graduate school education; being the mother of children younger than 18; and being the mother of children 18 and older. Lower health literacy was estimated based on the self-reported confidence in filling out medical forms ("extremely"/"quite a bit confident" vs. "a little bit"/"not at all").

Metrics for the patient-physician interaction included two summary scores extracted from survey items using principal component analysis, described in the Appendix. Briefly, a score for good communication with the physician was based on 3 items rating positive aspects of the patient-physician communication ["physician listens carefully", "patient feels encouraged to ask questions", "physician understands patient's background and values"] (Commonwealth Fund, 2001; Doescher et al., 2000), with higher scores for greater quality of communication. Similarly, a summary score for physician mistrust was based on 4 items rating the mistrust of the patient for her physician ["trust that medical needs are put above all else" [reverse coded], "physician is ordering unnecessary tests/procedures", "physician's decisions influenced by insurance", "doctor looks down on me"] (Commonwealth Fund, 2001; Doescher et al., 2000), with greater scores indicating greater mistrust.

Information on factors that may influence the decision of accepting or not chemotherapy were collected from the survey, and summarized as scores for family support (summary score based on 7 items relevant to family situation, family role in medical decision and family support

during the treatment, with greater score indicating greater support); opportunity cost of time, and worry about work (both based on 8 items measuring barriers for receiving chemotherapy, such as burden on activities or family, worrying about time off work, traveling time to medical center), with greater score indicating greater burden on time or work/activities (Degner et al., 1997a). Detailed description of the summary scores is provided in the Appendix. An indicator for reporting a higher opportunity cost of time was generated with value 1 for scores at the 75th percentile and above, and 0 for scores below the 75th percentile.

Finally, all models included a dummy variable for the year of testing, and took into account the clustering of patients by areas of residence (Core-based Statistical Areas (CBSA) from Census 2010, equivalent to metropolitan areas >10,000 residents) combined with a categorical variable for the four U.S. Census regions (northeast, North Central, South, and West); geographic information was collected from claims. As sensitivity analyses, all logit models were also estimated with clustering by CBSA and a set of indicators for U.S. states, resulting in similar results. Multilevel logistic regression was considered and rejected, based on an intraclass correlation less than 2%.

2.3.3 Statistical Analysis

Variable statistics are expressed as the mean ± standard deviation (SD) for continuous variable, and as frequency for categorical variables. Differences in means and in distribution between groups were tested using two-sided t-test or analysis of variance (ANOVA), and Pearson's chi-square, respectively. Summary scores were calculated using principal component analysis with optimization using the Varimax rotation method (see Appendix for details). Consistency of the scores with the items they represent was verified by correlation analysis.

Correlation between variables was tested by the significance of the pairwise correlation coefficients.

The influence of patient preferences for chemotherapy on risk perception was modeled using ordered logistic regression. To accommodate proportional odds, age and its squared value were conjointly used in this model, and the assumption of proportional odds was verified by performing a Brant test (Brant, 1990). The equation for the model is as follows:

$$Y_{RiskPerception} = \beta_0 + \beta_1 * \text{“preference for chemotherapy”} + \Sigma (\beta_i * \text{covariate}) + \varepsilon$$

where $Y_{RiskPerception}$ is the log odds for perceiving a higher risk of recurrence versus a lower risk of recurrence.

The effect of patient preferences and risk perception on the treatment decision was modeled using a series of logistic regression models that included 1) patient preferences for chemotherapy, 2) risk perception, or 3) both, with the following equations:

(1) $$Y_{\text{Treatment decision}} = \beta_0 + \tau * \text{“preference for chemotherapy”} + \Sigma (\beta i * \text{covariate}) + \varepsilon$$

(2) $$Y_{\text{Treatment decision}} = \alpha_1 * \text{“perceived risk”} + \Sigma (\alpha_i * \text{covariate}) + \varepsilon$$

(3) $$Y_{\text{Treatment decision}} = \beta'_0 + \tau' * \text{“preference for chemotherapy”} + \beta_1 * \text{“perceived risk”} + \Sigma (\beta'_i * \text{covariate}) + \varepsilon$$

where $Y_{\text{Treatment decision}}$ is the log odds for the probability of chemotherapy use.

The three models were run on the same sample corresponding to the full model. The methodology used to test for an indirect effect of patient preferences on treatment decision via risk perception is described in the Appendix (Baron and Kenny, 1986; Karlson et al., 2012; MacKinnon et al., 2000). Briefly, the coefficient estimates for patient preferences obtained in absence and in presence of risk perception (τ and τ‘, respectively) were compared. The

significance of the difference between the two coefficients (τ - τ‘) was tested using the Karlson-Holm-Breen method for nested nonlinear probability models, which decomposes the total effect of a variable into unbiased estimates for the direct and indirect components (Karlson et al., 2012).

Values were missing for 13% of reports on patient preferences, 2% of the reports on perceived risk, and less than 10% for the other covariates. All analyses were performed on complete cases. To test for potential selection bias from non-response, the characteristics of the complete cases were compared with those of the cases with missing values (Table 2.S1). Respondents with missing values were more often African American, were less often White, had lower SES, and lower rate of chemotherapy use compared to complete cases (Table 2.S1). Differences in geographic regions may relate to differences in SES, as women living in the West region tended to have higher SES, and women living in the Northeast tended to have lower SES. In the sample used to model the treatment decision, cases with missing values were younger and scored higher for opportunity cost of time (Table 2.S1, Sample 2).

Multivariate models were adjusted for patient characteristics (age, race/ethnicity, education, health literacy, income, health, good communication with the physician, physician mistrust, family support, opportunity cost of time, worry about work), year of testing and U.S. Census region; and patient clustering by areas of residence (CBSA); models for the probability of chemotherapy use were also controlled for the recurrence risk based on the genomic test. Robust estimates of the variance were obtained using the Huber-White sandwich estimator. Throughout the study, values were considered significant for P-value lower than 0.05. All analyses were performed on STATA 13 (Stata Corp., College Station, TX).

2.4 RESULTS

2.4.1 Patient characteristics

Demographic and clinical characteristics of the respondents are presented in Table 2.1. Characteristics are also presented with stratification by race and ethnicity because of the strong associations of age, SES and other patient characteristics, such as health literacy, with race/ethnicity in the setting of cancer care. The mean age of the patients was 52 years (SD 7; range 29-64), with 34% of the participants being aged less than 50. Asian patients were on average younger, with 48.5% aged less than 50. While the education level of the cohort was overall high, the frequency of lower education level (high school graduate or lower) was significantly higher among Hispanics. Lower household income (less than $40,000 annually) was significantly more frequent among Hispanic and Black women. Hispanic women more frequently reported a lower confidence in filling medical forms—the proxy measure for health literacy. Regarding patient-physician interaction, we found no significant differences in the score for good communication with the physician, but Asian women expressed significantly higher level of physician mistrust than the other groups (P= .007). Among factors that may influence treatment decisions, family support was significantly stronger for Hispanic patients, and lower for Black women; Hispanic and Asian women scored higher for opportunity cost of time; and Black women expressed significantly higher levels of worry about work (all P ≤.001).

Based on laboratory records, 55% of the patients were predicted to be at low recurrence risk, 35% at intermediate risk, and 10% at high risk (Table 2.1). No difference in recurrence risk was observed by race/ethnicity. As expected, use of chemotherapy varied significantly by recurrence risk, with low rate among the low-risk patients (8 %) and high rate among the high-

risk patients (89%). The use of chemotherapy among low-risk patients was marginally higher for Hispanic and Black patients than for Asians and Whites (P= .077).

2.4.2 Patient preference for chemotherapy

Patient preference for chemotherapy was measured as the numbers of additional years of life that would make chemotherapy worthwhile, based on a hypothetical lifetime of 10 years without chemotherapy (Mandelblatt et al., 2010; Ravdin et al., 1998). 87% of the respondents (n=777) answered the question, with 21% accepting chemotherapy for less than a 2-year gain, 14% selecting a 3–5 year gain, 14% a 6–10 year gain, and 39% willing to undergo treatment for a gain of more than 10 years; finally 12% responded that no numbers of years would be worthwhile (Figure 2.1).

Patient preference for chemotherapy varied significantly with age, race/ethnicity, education, income, health literacy, and health status (all significant at the 5% level; Table 2.2). Women expressing high chemotherapy preference (i.e., choosing gain of 2 years or less) were significantly younger (average age, 50.7 years versus 52.3 years, P= .007), more often White, had higher income and education levels, and reported better health (Table 2.2). High preference for chemotherapy was also significantly associated with higher score for the quality of communication with the physician and lower mistrust (average difference, .21 points and -.45 points, respectively, both P<. 05). Low preference for chemotherapy (i.e., choosing gain more than 10 years) was reported more often among African-Americans, women in poorer health, and women scoring higher on the metric for opportunity cost of time; reports of low preference were less frequent among women with higher education (Table 2.2). Women expressing complete aversion of chemotherapy (““no years worthwhile”) were more often Hispanic and Black, and less often White, reported poorer health, lower education and lower health literacy (Table 2.2).

Women averse to chemotherapy also scored significantly lower on the score for good communication with the physician, and higher on the score for mistrust (average difference, -.25 points and .49 points, respectively both P<. 05).

In contrast, there was no significant association of patient preference for chemotherapy with the recurrence risk based on the test (P = .384, Table 2.2). Patient preference for chemotherapy was only marginally associated with actual chemotherapy use during the treatment (P= 0.053, Table 2.2). Figure 2.2 shows the distribution of patient preference by treatment and risk recurrence, and choosing a gain greater than ten years was the dominant choice in all subgroups.

We focused on the women expressing low preference for chemotherapy (i.e., choosing a gain more than 10 years; 39% of the question respondents, Table 2.2). We reasoned that in case of low preference for chemotherapy, the treatment decision would be more sensitive to other factors (e.g., strength of the doctor recommendation, family opinion, community values), whereas an extreme preference (high preference, or aversion) may dominate the willingness to undergo treatment. We also reasoned that the influence of risk perception on the decision might be stronger for women who reported low preference compared to women with more affirmed preferences (high preferences, or aversion). Therefore, we dichotomize the patients based on the report of low preference versus all the other categories of patient preferences for chemotherapy. This indicator for the propensity to express low preference for chemotherapy is used here as a proxy measure for unobserved patient characteristics, such as experience with chemotherapy received by relatives or friends, cultural values, or health beliefs.

2.4.3 Patient reports on risk perception

874 patients (97% of the respondents) reported on their risk perception, measured as the chance of recurrence at 10 years. 25% of the women reported a very low chance, 34% a low chance, 30% a moderate chance, and 11% a high/very high chance (Table 2.3). Perceived risk was significantly correlated with the laboratory-based recurrence risk categories (rho= .1237, P < .002). [The supplemental material shows a comparison of the measures of patient perceived risk with the objective risk based on laboratory results.]

Risk perception varied significantly by age, self-reported health, objective recurrence risk predicted by the test, and preference for chemotherapy (Table 2.3). Lower risk perception was associated with younger age, better health, and lower laboratory-based predicted risk (all, P <. 05; Table 2.3). Higher risk perception was associated with higher preference for chemotherapy, and patient reporting low preference for chemotherapy were less often reporting high/very high risk perception (P= .037; Table 2.3).

We use ordered logistic regression to analyze the association of risk perception with patient preference for chemotherapy, controlling for age, race/ethnicity, education and other patient characteristics (Tables 2.4 and 2.S2). Based on the ordered logistic model, after controlling for other factors and clustering, lower levels of chemotherapy preference were significantly associated with lower risk perception (Table 2.4, model 2). Low preference for chemotherapy was also significantly associated with perceiving lower level of risk (Table 2.4, model 3). Education and health literacy were significant in all models (Table 2.4). Lower education was associated with an elevated risk perception, and lower health literacy was associated with lower risk perception. Hispanic women were more likely to report risk at a higher level than White women, and the effect was significant when controlling for chemotherapy preference (Table 2.4,

model 1 versus models 2 and 3). Black women were more likely to report lower risk than White women (model 1), but the effect was only marginally significant and disappeared after controlling for patient preference for chemotherapy.

2.4.4 Variations in the probability of receiving chemotherapy by patient preference and risk perception

We found a significant association of risk perception and patient preference for chemotherapy. We hypothesized that the effect of patient preference for chemotherapy may act indirectly on the treatment decision through the filter of risk perception. In this model, women who express low preference for this treatment may accept the treatment if they feel that the risk of recurrence makes chemotherapy worthwhile, whereas they may decide not to undergo treatment if they perceive a lower risk.

To test for an indirect effect of chemotherapy preference on the treatment decision through risk perception, we needed to establish that chemotherapy preference has an effect on risk perception (as shown above), and that both chemotherapy preference and risk perception had a significant effect on the decision. Using a series of logistic regressions, we showed that risk perception and low preference each have a significant effect on the treatment decision (Table 2.5 and Table 2.S3). Perceiving high or very high risk of recurrence increased the odds of chemotherapy use three fold, and low preference for chemotherapy was also associated with higher odds of chemotherapy use (OR 1.17, 95% CI [1.10, 2.65]). When the two factors were combined both corresponding coefficient estimates were significant (Table 2.5). We tested the role of risk perception in a mediation path between patient preferences and treatment decision

using the Karlson-Holm-Breen method, or KHB method (Karlson et al., 2012). The KHB method aims to decompose the direct effect and indirect effect of a variable by comparing estimates from same-sample nested models. To show the indirect effect of X on Y via Z, the model including both X and Z is compared with a model including X and the residuals of a linear regression of Z on X. Including the residuals results in unbiased estimates for the direct and total effect of X on Y, and allows for testing the significance of the effect on X via Z (Karlson et al., 2012; MacKinnon et al., 2000). In this set up, a significant effect indicates mediation if the difference between total effect and direct effect is positive; and suppression if the difference is negative (MacKinnon et al., 2000).

We ran the –khb– module to implement the Karlson-Holm-Breen method in STATA 13. The models produced results similar to those presented above for the probability of chemotherapy use (Table 2.6). Figure 2.3 summarizes the result of the models used to test for mediation. We examined the difference in the coefficients for patient preference (here, low preference for chemotherapy) between the models including either risk perception or the residuals. Using the delta method, the difference in coefficients was found significant, supporting the existence of the mediation path. Also the difference was negative ($\tau - \tau' = -0.68$, P= .041), indicating that risk perception has a suppressing effect on patient preferences. In conclusion, the result supports the hypothesis that a patient's low preference for chemotherapy may influence the treatment decision through the filter of risk perception, and its inclusion in the model reveals the unbiased effect of the patient preferences on the treatment decision.

2.5 DISCUSSION

We analyzed the relationship between patient preferences, risk perception and treatment decision using patients' reports from a retrospective survey on their breast cancer care. We found

significant relationships between patient preferences for chemotherapy and risk perception, patient preferences for chemotherapy and treatment decision, and risk perception and treatment decision, respectively.

We found significant variations in preferences for chemotherapy by patient characteristics, including health status, age, race/ethnicity and SES, whereas there was no significant association with the recurrence risk predicted by a genomic test, or with the actual use of chemotherapy during the treatment. In this cohort, 39% of the patients expressed a low preference for chemotherapy by indicating that gains in life years greater than 10 years would make six months of chemotherapy worthwhile. These results contrast with other studies where patients reported to be willing to accept a treatment even if the benefit was very small (Duric et al., 2007; Duric et al., 2005; Hamelinck et al., 2014; Lindley et al., 1998; McQuellon et al., 1995; Simes and Coates, 2001). It is possible that the measure of patient preferences in a retrospective study was influenced by the treatment received by the patients, despite the lack of significant association between patient preferences and treatment received (Table 2.2). The mode of administration of the question (1 question in a mailed survey, with a choice between 5 response items) may compromise the comparability with other studies that used an interview setting with a series of questions offering decreasing gains in life years. Also, the patients in this study were all diagnosed at stage I or II, with negative lymph nodes, whereas other studies of preferences for early-stage breast cancer included also patients at stage III and patients with positive lymph nodes (Duric et al., 2007; Simes and Coates, 2001). Still, we cannot exclude that the treatment decision and the risk perception itself may have influenced the retrospective report of patient preferences, and this issue will need to be addressed in future studies using a prospective design.

As expected, variations in risk perception were significantly associated with education, health literacy, and patient preference for chemotherapy treatment. We detected no significant effect of age in this population that was relatively young (average age, 52) and often part of the work force (52% worked full time). We also found variations by race/ethnicity. The likelihood of reporting more elevated levels of risk perception was higher for Hispanic women than for White women after controlling for education, health literacy and other factors, and we found a trend towards reporting lower level of risk perception among Black women. Those results are consistent with other studies finding that Hispanic women are more likely to perceive higher level of risk, and that Black women may be at risk of underestimating their chance of disease (Brewster et al., 2007; Haas et al., 2005; Janz et al., 2011).

To analyze the mechanisms underlying the influence of patient preferences and risk perception on the treatment decision, we posited that the propensity for low chemotherapy preference might capture unobserved patient characteristics that impact the treatment decision when there is medical uncertainty about what is the optimal treatment option. In this framework, a patient with low preference for chemotherapy may be influenced in her decision to accept or refuse the treatment through the filter of risk perception. If the risk is perceived to be high, the patient may be more likely to accept the treatment, and if the risk is perceived to be low, she may be more likely to decline. In this model the total effect of the low chemotherapy preference is decomposed into two components affecting the decision, a direct effect and an indirect effect via risk perception. Our findings support this model, as the estimate for the indirect effect was found to be significant; also, the negative sign indicates a suppression effect. Our results support that the low preference for chemotherapy influence the treatment decision through the filter of risk perception. As both patient preferences and risk perceptions are characteristics that are

changeable, they provide targets for intervention that may help in improving shared decision-making.

Previously, DeFrank and colleagues (2013a) have proposed that risk perception may mediate the effect of the recurrence score predicted by the genomic test on the treatment decision. Our results do not exclude the convergence of diagnostic information and patient preferences on risk perception, and we found a significant association of risk perception and objective risk based on the test result. The relationship between information exchange and risk perception is important to explore in future studies as risk perception has also been offered to moderate the relationship between communication and decision (Epstein and Street, 2007).

This study has a number of strengths to address the effects of patient preferences and risk perception on the treatment decision. First, the survey provides detailed reports on the patient characteristics and attitudes during treatment strategy in a large, diverse sample. The oversampling of minority patients resulted in a sufficient analytic power to look at individual racial/ethnic groups, and allowed us to detect effects that would have been masked by aggregating all non-White patients together. Also, the use of two different measures of patient-perceived risk of recurrence (in words and in numbers) helped in assessing the validity of the information collected in the survey. We limited the analysis to the use of the measure of risk perception in words, as it seemed more consistent than the measure expressed in numbers. Another study selected also the risk perception in words only, based on evidence that a narrative framing may be more comprehensible to the general public than probabilistic information (Nelson et al., 2008; Waters et al., 2010). More recently, Retel and colleagues (2013) have used the numeric format to measure risk perception among breast cancer patients who had received the Mammaprint genomic test 6–8 weeks before, and they found no significant differences in

risk perception between risk groups based on the test results. In contrast, DeFrank and colleagues (2013a) found a strong association between perceived risk expressed as 0–100% chance and the genomic test result in a study of breast cancer survivors asked to evaluate vignettes. Those variations in results suggest that more research is needed to establish a standardized measure for risk perception that may help in comparing effect between studies. However, the validity of our measure of risk perception is supported by replicating the findings of associations with education, health literacy and patient preferences shown by other studies.

Limitations of the study include the retrospective study design, and the problem of omitted clinical variables, including tumor stage and family history of cancer that are likely to influence risk perception. An important concern is that risk perception measured retrospectively may be an imperfect measure if it was influenced by the treatment experience. It is possible that a patient who did not receive chemotherapy during her treatment may perceive a lower risk than if she had, because the treatment was less aggressive; but it is also possible that after receiving chemotherapy, a patient may feel at lower risk of recurrence with this additional treatment. Furthermore, it is possible that different subgroups of patients may feel differently based on their treatment experience. This is an issue that cannot be addressed with a retrospective study design, and future studies would need to document patient risk perception before learning about the test result to better understand the effect of risk perception on the treatment decision. Exclusion criteria for the study eligibility included having a previous history of breast cancer or other cancer, based on health plan information, which limited the possibility of a patient's prior experience of chemotherapy; but it is possible that information may be lacking about treatment received before enrolling in this health plan. The regression analyses were performed on

complete cases only, and the women with missing values were more often African Americans and at lower SES than the complete cases (Table 2.S1); also, patients with missing values had less often received chemotherapy, so it is likely that if there is a selection bias, the bias of the estimates would be toward zero.

The mode of the survey, mailed and self-administered, imposed space constraints on the numbers of questions that could be included. As mentioned above, the time trade-off used to evaluate patient preference for chemotherapy was limited to one question in the survey, which may limit the comparability with other studies. Health literacy was measured as the patients' report of confidence in filling medical forms, which may be limited for capturing such a complex concept. In the absence of standard methods for measuring health literacy in a mailed survey, we selected this question that relates to different skills involved in health literacy (reading, understanding and formulating choices for medical). A similar approach for measuring health literacy was used in a mailed survey asking patients about their experience and understanding of the genomic test (Tzeng et al., 2010).

Finally, the study was limited to a privately insured population, aged less than 65 with overall a high socio-economic status. It is difficult to determine if our findings would apply to an older population, or to patients with lower resources.

Measured retrospectively, the differences in risk perception observed in this study may be relevant for other outcomes of care. Higher perceived risk is associated with lower mental and physical quality of life of cancer survivors (Waters et al., 2010). A similar effect was recently found in a study of women who had received the genomic test during their breast cancer treatment (Retel et al., 2013). Risk perception may also influence health behaviors, and has been

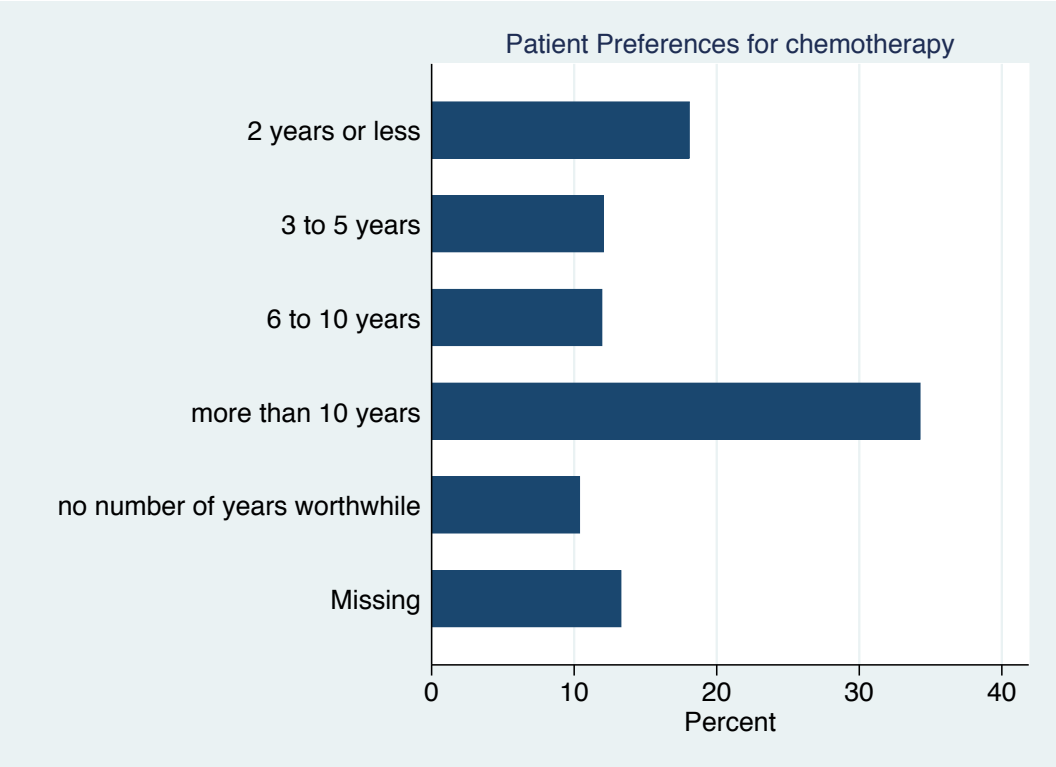
identified as a cause of health disparities. For instance, in the 2007 Health Information National Trends Survey (HINTS), the perceived risk of cancer was lower among Latinos than among Whites, and lower risk perception was associated with less frequent reporting of a family history of cancer (Orom et al., 2010). In turn, a study of the 2005 California Health Interview Survey identified that a lack of knowledge about family history was associated with lower level of colon cancer screening among Latinos (Ponce et al., 2012). Similarly, variations in risk perception were found to contribute to lower use of mammography and genetic screening (Armstrong et al., 2005; Haggstrom and Schapira, 2006).

Risk perception is a mutable factor, and is sensitive to information (Epstein and Street, 2007). Helping women assess their risk of recurrence more accurately may help in supporting adherence to surveillance and hormonal therapy. It may also help engage in protective behaviors, such as maintaining a healthy body mass index that was identified as a cause of disparities among long-term breast cancer survivors (White et al., 2013). Unfortunately, risk perception and knowledge may not be sufficient to engage in risk-lowering behavior. A study of 186 breast cancer survivors who had received the genomic test found that most women were aware of health behaviors reducing the risk of cancer, but few were engaging in those behaviors (O'Neill et al., 2013). In particular, women at intermediate and high risk of recurrence were not more likely to adopt protective behaviors. In this study, perceived risk of recurrence was also not significantly associated with healthier behaviors. While those results need to be confirmed by others, they suggest that knowledge and perception of risk may not be sufficient, and that patient support is needed to initiate and maintain lifestyle changes. Another important element in cancer secondary prevention is the adherence to hormonal therapy, and there is evidence that adherence to hormonal therapy is lower among breast cancer patients who perceive lower benefits of the

treatment (Fink et al., 2004). It is unknown if adherence to hormonal therapy is different for women who received the test compared to those who did not. This is an important issue as the prediction of the recurrence risk based on the genomic test is conditional on patient adherence to hormonal therapy for at least 5 years. Future research should examine if the genomic test has an impact on adherence to hormonal therapy, and to identify ways to promote the use of risk-lowering behaviors among women who received the test.

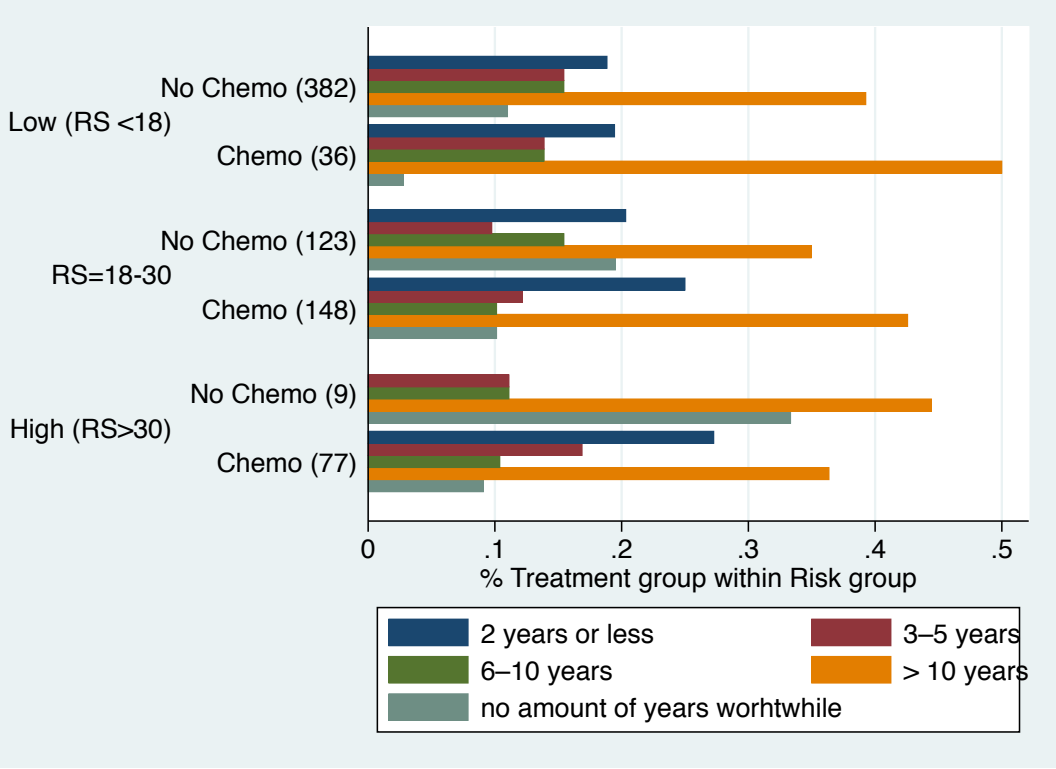
2.6 FIGURES AND TABLES

Figure 2.1: Distribution of patient preferences for chemotherapy.



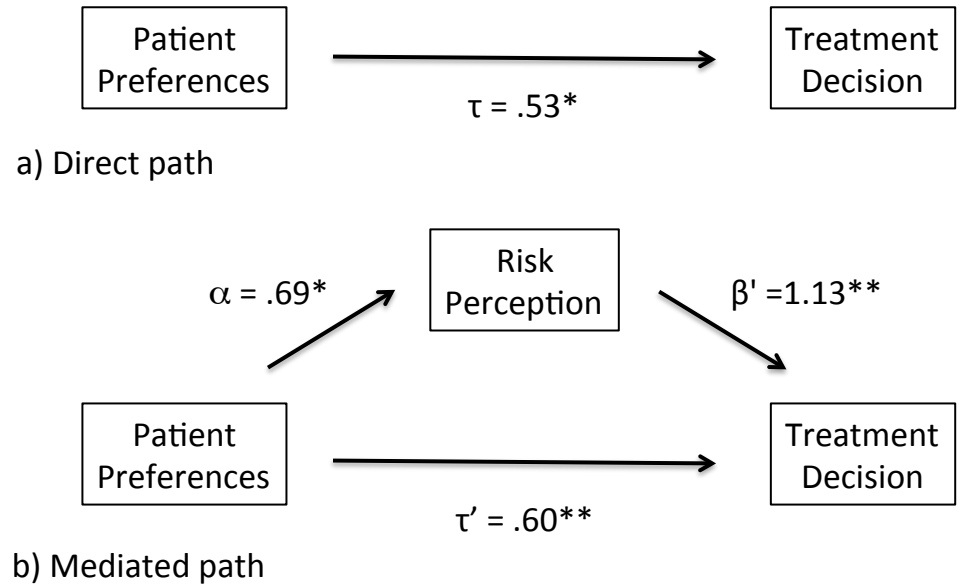
Distribution in percent (n= 896). Missing indicates the percentage of patients who did not answer to this question.

Figure 2.2: Patient preferences for chemotherapy after stratification by recurrence risk and treatment.



Patient reports on how many additional life years would make worthwhile six months of chemotherapy is shown by treatment subgroup (chemotherapy use or no) within the three recurrence risk categories (low for RS <18, intermediate for RS =18–30, and high for RS >30). The number of patients in each treatment subgroup is indicated in parentheses. The bar graph shows the distribution of preferences in percent within each treatment subgroup. In all subgroups, patients predominantly choose the item “more than 10 years”.

Figure 2.3: Risk perception suppresses the relationship between patient preferences and treatment decision



* p <.05. ** p<.01

a) Direct path: the unbiased estimate for the total effect of low preference for chemotherapy (τ =.53*) was measured using residual inclusion (Table 2.5).

b) Mediated path: the direct effect of patient preferences was estimated as the coefficient for low preference (τ' =.60**), and a significant indirect effect is obtained for high/very high risk perception (β' =1.13**, Table 2.5). The coefficient estimate for the effect of low preference for chemotherapy on risk perception (α = .69*) was obtained in Model 3 of Table 2.6.

The hypothesis that risk perception is involved in a mediation pathway between patient preference (here, low preference for chemotherapy) and treatment decision is supported by the significance of the difference $\tau - \tau'$ =-.068* (Table 2.6), using the Karlson-Holm-Breen method (2010).

Table 2.1: Participant characteristics, overall and by race/ethnicity

Characteristics	All Women n = 896†	Hispanic n = 108 (12.1%)	Black n = 112 (12.6%)	Asian n = 97 (10.9%)	White n = 549 (61.7%)	Other[1] n = 24 (2.7%)	*P*
Age at test	52.0 (7.0)	51.2 (7.3)	52.3 (6.9)	49.9 (7.0)	52.5 (6.8)	50.8 (7.6)	**.007**
< 50 years	301 (34%)	44 (41%)	37 (33%)	47 (49%)	164 (30%)	9 (38%)	**.003**
≥ 60 years	146 (16%)	17 (18%)	17 (15%)	11 (11%)	98 (18%)	3 (13%)	**.545**
Education							**<.001**
≤ High school	115 (13%)	23 (21%)	13 (12%)	2 (2%)	75 (14%)	2 (8%)	
College	556 (62%)	67 (62%)	72 (64%)	67 (69%)	339 (62%)	11 (46%)	
Grad. school	218 (24%)	18 (17%)	27 (24%)	27 (28%)	135 (25%)	11 (46%)	
Income							**<.001**
<$40,000	105 (12%)	22 (20%)	25 (22%)	7 (7%)	49 (9%)	2 (8%)	
$40,000-74,999	190 (21%)	38 (35%)	36 (32%)	15 (16%)	98 (18%)	3 (13%)	
$75,000-149,999	305 (34%)	23 (21%)	25 (22%)	19 (20%)	150 (27%)	8 (33%)	
≥ $150,000	235 (26%)	15 (14%)	14 (13%)	37 (38%)	163 (30%)	6 (25%)	
Low health literacy	41 (5%)	13 (12%)	3 (3%)	7 (7%)	17 (3%)	1 (4%)	**<.001**
Opportunity cost of time							**<.001**
< 75th percentile	593 (75%)	63 (64%)	68 (72%)	50 (58%)	394 (80%)	18 (82%)	
≥ 75th percentile	201 (25%)	36 (36%)	27 (28%)	37 (42%)	97 (20%)	4 (18%)	
Children < 18 y	220 (25%)	31 (29%)	14 (13%)	33 (34%)	137 (26%)	5 (21%)	.054
Children ≥ 18 y	543 (61%)	67 (62%)	79 (71%)	51 (53%)	328 (60%)	13 (54%)	.327
Health							
Excellent	174 (20%)	17 (16%)	20 (18%)	15 (16%)	121 (225)	1 (4%)	.126
Very good	399 (46%)	44 (41%)	46 (42%)	45 (48%)	254 (47%)	10 (42%)	
Good	246 (28%)	35 (33%)	34 (31%)	29 (31%)	137 (25%)	11 (46%)	
Fair	58 (7%)	11 (10%)	10 (9%)	5 (5%)	30 (6%)	2 (8%)	
Recurrence risk from Test							.289
Low (RS<18)	492 (55%)	54 (50%)	56 (50%)	54 (56%)	315 (57%)	11 (46%)	
Intermediate	310 (35%)	42 (39%)	35 (31%)	36 (37%)	184 (34%)	10 (42%)	
High (RS> 30)	92 (10%)	11 (10%)	21 (19%)	7 (7%)	49 (9%)	3 (13%)	
Chemotherapy use (% within each risk group based on test)							
Low	37 (8%)	8 (15%)	6 (11%)	1 (2%)	22 (7%)	0 (0%)	**.077**
Intermediate	161 (52%)	23 (55%)	20 (57%)	18 (50%)	95 (52%)	5 (50%)	.967
High	82 (89%)	11 (100%)	17 (81%)	7 (100%)	43 (88%)	3 (100%)	.397
Year of treatment							.866
2009	115 (13%)	13 (12%)	13 (12%)	16 (16%)	70 (13%)	3 (135)	
2010	197 (22%)	22 (21%)	23 (21%)	20 (21%)	125 (23%)	4 (17%)	
2011	267 (30%)	39 (36%)	30 (27%)	26 (27%)	164 (30%)	6 (25%)	
2012	315 (35%)	33 (31%)	46 (41%)	35 (36%)	189 (34%)	11 (46%)	
U.S. Census region							**<.001**
Northeast	205 (23%)	20 (19%)	28 (25%)	26 (27%)	125 (23%)	2 (8%)	
North Central	100 (11%)	4 (4%)	8 (7%)	5 (5%)	80 (15%)	1 (4%)	
South	430 (48%)	65 (60%)	73 (65%)	35 (36%)	244 (44%)	13 (54%)	
West	159 (18%)	18 (17%)	3 (3%)	31 (32%)	99 (18%)	8 (33%)	

Continuous variables, mean (SD); categorical variables, frequencies (percent given by columns).

Differences in means between racial/ethnic groups tested using ANOVA, and differences in distribution tested using Pearson's chi-square, with significance for P < .05. Missing values < 5%, except for income (7% missing). Race/ethnicity is based on self-report and recoded as 5 mutually exclusive categories; † race/ethnicity is unknown for 6 respondents; claims and laboratory data are missing for 2 respondents (0.2%). [1] Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Table 2.2: Patient preference for chemotherapy

	Patient Preference for Chemotherapy					
	≤ 2 years	**3-5 years**	**6-10 years**	**> 10 years**	**No years**	**P**
Overall (n=777)	162 (21%)	108 (14%)	107(14%)	307 (39%)	93 (12%)	
Age						**.026**
≥ 60	17 (13%)	13 (10%)	26 (20%)	55 (43%)	16 (13%)	
< 60	145 (22%)	95 (15%)	81 (12%)	252 (39%)	77 (12%)	
Race/Ethnicity						**<.001**
Hispanic	13 (14%)	9 (9%)	8 (8%)	42 (44%)	24 (25%)	
Black	10 (12%)	0	8 (9%)	48 (56%)	19 (22%)	
Asian	11 (13%)	4 (5%)	19 (22%)	37 (44%)	14 (16%)	
White	124 (26%)	88 (18%)	69 (14%)	170 (35%)	34 (7%)	
Other	3 (14%)	6 (29%)	3 (14%)	8 (38%)	1 (5%)	
Education						**<.001**
≤ High School	23 (24%)	9 (9%)	11 (11%)	33 (34%)	21 (22%)	
College	81 (17%)	64 (14%)	61 (13%)	213 (45%)	55 (12%)	
Graduate School	57 (28%)	34 (17%)	35 (17%)	59 (29%)	16 (8%)	
Income						**.003**
Low income	11 (14%)	8 (10%)	9 (11%)	38 (47%)	15 (19%)	
Mid income	83 (19%)	59 (13%)	59 (13%)	179 (41%)	58 (13%)	
High income	60 (28%)	36 (17%)	33 (15%)	70 (33%)	15 (7%)	
Lower Health Literacy						**.006**
Yes	1 (3%)	5 (14%)	6 (17%)	13 (37%)	10 (29%)	
No	160 (22%)	102 (14%)	100 (14%)	291 (30%)	82 (11%)	
Kids aged <18						**.006**
Yes	56 (29%)	30 (15%)	24 (12%)	71 (36%)	14 (7%)	
No	103 (18%)	76 (13%)	79 (14%)	231 (41%)	79 (145)	
Kids aged ≥ 18						**.466**
Yes	88 (19%)	63 (14%)	62 (13%)	193 (42%)	59 (13%)	
No	71 (24%)	43 (14%)	41 (14%)	109 (37%)	34 (11%)	
Opportunity cost of time						**<.001**
< 75th percentile	137 (25%)	90 (16%)	80 (15%)	194 (35%)	46 (8%)	
≥ 75th percentile	25 (11%)	18 (8%)	27 (12%)	113 (49%)	47 (20%)	
Health						**.017**
Excellent	45 (30%)	25 (16%)	16 (11%)	57 (38%)	9 (6%)	
Very Good	74 (21%)	45 (13%)	54 (16%)	136 (39%)	38 (11%)	
Good	32 (15%)	33 (15%0	29 (13%)	89 (41%)	33 (15%)	
Fair/poor	7 (14%)	5 (10%)	7 (14%)	22 (43%)	10 (20%)	
Recurrence Risk from Test						.384
Low	79 (19%)	64 (15%)	64 (15%)	168 (40%)	43 (10%)	
Intermediate	62 (23%)	30 (11%)	34 (13%)	106 (39%)	39 (14%)	
High	21 (24%)	14 (16%)	9 (10%)	32 (37%)	10 (12%)	
Chemotherapy Receipt						.053
Yes	65 (25%)	36 (14%)	28 (11%)	109 (42%)	23 (9%)	
No	97 (19%)	72 (14%)	79 (15%)	197 (38%)	69 (13%)	

Percentage by rows, and distribution tested using Pearson's chi-square. P < .05 indicates a significant variations in patient preferences for the characteristic of interest. Patient preference for chemotherapy was measured using a time trade-off of 6 months of chemotherapy for additional years of life based on 10 years of life without chemotherapy; measure is missing for 119 respondents out of 896 (13%).
Age and chemotherapy use were collected in claims data. Recurrence risk is based on the laboratory records. Other data are self-reports from the survey. No significant variations in patient preferences were detected by age category "less than 50" vs. "50 and more", type of health plan, year of testing, U.S. regions, and by scores for family support and worry about work.

Table 2.3: Risk perception

	Risk Perception				
	Very Low	**Low**	**Moderate**	**High/Very High**	**P**
Overall (n=880)	221 (25%)	303 (34%)	258 (30%)	96 (11%)	
Age *					**.043**
< 50	84 (29%)	84 (29%)	87 (29%)	38 (13%)	
≥50	137 (23%)	219 (37%)	171 (29%)	58 (10%)	
Health					**.009**
Excellent	61 (35%)	56 (32%)	40 (23%)	16 (9%)	
Very good	98 (25%)	138 (35%)	119 (30%)	39 (10%)	
Good	50 (20%)	91 (37%)	77 (31%)	27 (11%)	
Fair/Poor	7 (13%)	18 (32%)	20 (36%)	11 (20%)	
Race/Ethnicity					.194
Hispanic	19 (18%)	35 (33%)	35 (33%)	16 (15%)	
Black	39 (36%)	33 (31%)	26 (24%)	10 (9%)	
Asian	30 (32%)	28 (295)	26 (27%)	11 (12%)	
White	126 (23%)	198 (36%)	164 (30%)	55 (10%)	
Other	5 (22%)	8 (35%)	7 (30%)	3 (13%)	
Recurrence Risk from Test					**.007**
Low	135 (28%)	178 (37%)	127 (26%)	45 (9%)	
Intermediate	69 (23%)	101 (33%)	102 (33%)	33 (11%)	
High	17 (19%)	24 (28%)	29 (33%)	18 (20%)	
Patient Preferences					**.017**
≤ 2y (High Preference)	26 (23%)	55 (34%)	47 (29%)	22 (14%)	
3-5 y	16 (15%)	30 (28%)	43 (40%)	18 (17%)	
6-10 y	20 (19%)	47 (44%)	30 (28%)	10 (9%)	
> 10 y (Low Preference)	84 (27%)	108 (35%)	92 (30%)	23 (7%)	
No years worth (Aversion)	27 (30%)	26 (29%)	27 (30%)	11 (12%)	

Percent by row. Significant P values (less than .05) indicate significant variations in risk perception for the characteristic of interest using Pearson's chi-square. Top row shows the distribution of risk perception for the whole cohort. Information on risk perception is missing for 16 respondents out of 896 (2%). Variations in risk perception were also significant using the indicator corresponding to low preference for chemotherapy (P =.037). Recurrence risk is the risk predicted by the genomic test (laboratory records). Age was collected in claims data. Other data are self-reports from the survey. No significant variations in risk perception were detected by education, income, health literacy, kids age, quality of communication, physician mistrust, opportunity cost of time, family support, worry about work, type of health plan, year of testing, and U.S. region. * Stratification of patients using age 60 as a threshold was not associated with significant variations in risk.

Table 2.4: Variations in risk perception by patient preferences and demographic characteristics

Odds ratios for the variables significant at the 5% level in at least one model; full sets of estimates are presented in Table 2.S2. Odds ratio greater than 1 indicate that the variable is associated with higher risk perception. The logistic regression models were run on the same sample to test the significance of the association of chemotherapy preference and risk perception (comparing model 1 and model 2). We also tested the association of the propensity to report low preference for chemotherapy as a proxy measure for latent patient characteristics that may influence risk perception (model 3).

Risk Perception	**Model 1**		**Model 2**		**Model 3**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Patient characteristics						
≤ High school graduate	**2.07****	**[1.31,3.26]**	**2.13****	**[1.32,3.42]**	**2.00****	**[1.25,3.22]**
Lower health literacy	**0.42***	**[0.20,0.89]**	**0.45***	**[0.21,0.95]**	**0.42***	**[0.20,0.90]**
Race/Ethnicity						
White (ref.)	1	-	1	-	1	-
Hispanic	**1.49**	**[0.99,2.24]**	**1.69***	**[1.09,2.62]**	**1.53***	**[1.00,2.34]**
Black	0.62	[0.36,1.07]	0.76	[0.43,1.36]	0.68	[0.40,1.16]
Asian	0.78	[0.52,1.15]	0.88	[0.59,1.31]	0.8	[0.54,1.17]
Other	1.31	[0.52,3.29]	1.23	[0.49,3.08]	1.28	[0.50,3.29]
Chemotherapy Preference						
< 2y (High preference)			0.63	[0.39,1.02]		
3–5 y (ref.)			1	-		
6–10y			**0.56***	**[0.33,0.96]**		
> 10 (Low Preference)			**0.43*****	**[0.26,0.71]**		
No years worth (Aversion)			**0.43***	**[0.23,0.82]**		
Propensity for low preference					**0.69***	**[0.52,0.93]**

* P<0.05, ** p<0.01, *** p<0.001

N= 728 complete cases. The base outcome is “very low” perceived risk, compared to low, moderate, and high/very high. Only significant odds ratios are presented here, with 95% confidence intervals and significance of the P values for the individual Wald tests. Complete sets of estimates are presented in Table 2.S2. The models are adjusted for age, income, education, health literacy, communication with the provider, physician mistrust, year of testing, and U.S. region, with clustering adjustment by areas of residence (clusters= 160 CBSA). Age was collected in claims data. Other data are self-reports from the survey.

Table 2.5: Comparison of the effects of risk perception and chemotherapy preference on the odds of receiving chemotherapy

Odds ratios for the variables significant at the 5% level in at least one model; full sets of estimates are presented in Table 2.S3. Odds ratio greater than 1 indicate that the variable is associated with higher risk perception. The logistic regression models were run on the same sample to test the significance of the association of chemotherapy use with patients characteristics and clinical information (model 1), risk perception (model 2), low chemotherapy preference (model 3), and both risk perception and low preference (model 4). All models were run on the same sample of complete cases (n= 677).

Chemotherapy Use	**Model 1 Base**	**Model 2 Risk Perception**	**Model 3 Low Preference**	**Model 4 Full Model**
	OR	**OR**	**OR**	**OR**
Age	**0.95***	**0.95***	**0.95****	**0.95****
Recurrence risk				
Low	1	1	1	1
Intermediate	**12.73*****	**12.74*****	**13.13*****	**13.17*****
High	**113.80*****	**109.34*****	**118.24*****	**112.95*****
Communication	**0.75**	**0.75**	**0.71***	**0.71***
Opportunity cost	**0.71****	**0.71****	**0.67****	**0.66*****
Perceived risk				
Very low (Ref.)		1		1
Low		1.47		1.47
Moderate		1.77		1.83
High/Very High		**2.83****		**3.09****
Low preference for chemotherapy			**1.71***	**1.83****

* P<0.05, ** p<0.01, *** p<0.001

N=677 complete cases. Odds Ratios and significance of the P-value for the individual Wald tests. All models are controlled for age, income, education, health literacy, communication with the provider, physician mistrust, family support, worry about work, type of health plan, year of testing, and U.S. region, with clustering adjustment by areas of residence (clusters= 152 CBSA). Full models are presented in Table 2.S3. Recurrence risk is the category of risk predicted by the genomic test (laboratory records). Age was collected in claims data. Other data are self-reports from the survey.

Table 2.6: Test for the indirect effect of patient preference for chemotherapy on treatment decision via risk perception using the Karlson-Holm-Breen method

Treatment Decision	**Direct + indirect effects**			**Total effect**		
	Beta	**SE**	**P**	**Beta**	**SE**	**P**
Age	-.05**	.02	.009	-.05**	.02	.008
Recurrence risk from test						
Low (ref.)	0			0		
Intermediate	2.58***	.28	< .0001	2.62***	.28	< .0001
High	4.73***	.48	< .0001	4.86***	.48	< .0001
Communication	-.34*	.16	.032	-.34*	.16	.032
Opportunity cost of time	-.41*	.12	.001	-.41*	.12	.001
Low chemotherapy preference	**.60****	**.22**	**.006**	**.53***	**.22**	**.016**
Perceived risk						
Very Low (ref.)	**0**	**-**	-			
Low	**.38**	**.30**	**.199**			
Moderate	**.60**	**.35**	**.088**			
High/Very High	**1.13****	**.38**	**.003**			
Residuals for Z on X						
---001				**.38**	**.30**	**.199**
---002				**.60**	**.35**	**.088**
---003				**1.13****	**.38**	**.003**
Chi2	257.71			257.71		

* P<0.05, ** p<0.01, *** p<0.001

N=677 complete cases. The difference between the coefficients for Low preference in the two models (total – direct) is an estimate of the indirect effect of low preference on the treatment decision through risk perception. The KHB method produces an unbiased estimate of the difference using the delta method: difference, -.068 (SE .033) with 95% CI [-.133, -.003]. The percentage change in coefficient is -13%. The two models are also controlled for income, education, health literacy, physician mistrust, family support, worry about work, type of health plan, year of testing, and U.S. region, with clustering adjustment by areas of residence (clusters= 152 CBSA). Only significant coefficients are presented in the table.

2.7 SUPPLEMENTAL MATERIAL

2.7.1 Methods—Mediation and suppression

To test for the effect of a third variable (here, risk perception) as part of the effect of an independent variable X (here, patient preference for chemotherapy) on the outcome Y (here, the treatment decision), three criteria are required: 1) X has a significant effect on Y; 2) X has a significant effect on Z; 3) Z has a significant effect on Y in a model that includes X (Baron and Kenny, 1986; MacKinnon et al., 2000). An indirect effect of X on Y through Z is shown by comparing the effect of X on Y in the absence and in the presence of Z. Finding that the effect of X on Y is significantly greater in the absence of Z, indicates mediation; if the effect of X is increased in presence of Z, it supports a suppression effect (MacKinnon et al., 2000).

The significance of the difference between the two coefficients can tested using the Karlson-Holm-Breen method for same-sample, nested nonlinear probability models, which decomposes the total effect of X into its direct and indirect components in an unbiased way (Karlson et al., 2012). To do so, two models are run in parallel, one including Z, and the other including the residuals from the linear regression of Z on X. In the model including Z, part of the effect of X is direct, the other is captured by Z (indirect effect); in the model including the residuals only, all the effect, or total effect, goes through X. The difference between the coefficients for X obtained in the two models (total minus direct) gives a unbiased estimates for the indirect effect of X via Z, and P-values and 95% confidence intervals are produced using the delta method.

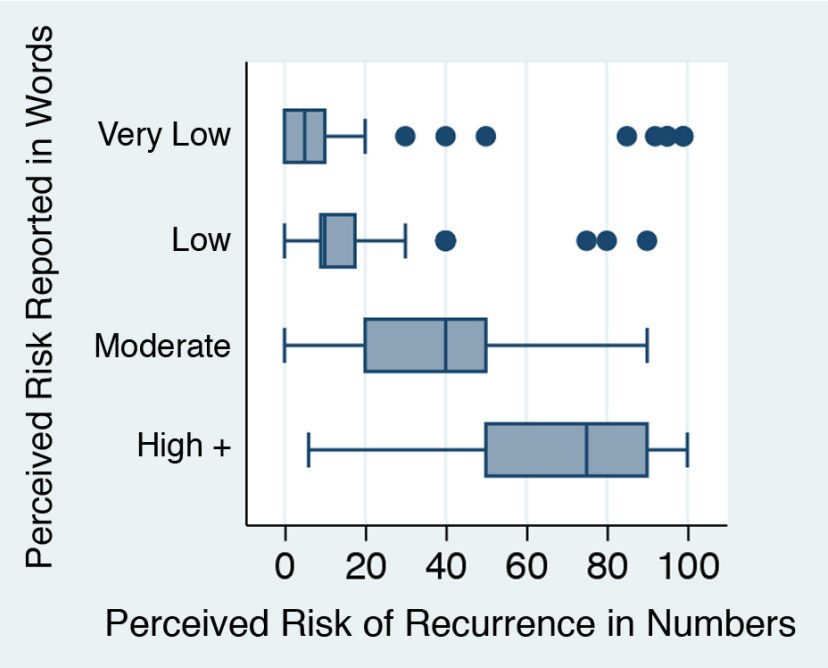
2.7.2 Results—Comparison of the patient reports on risk perception in words and numbers

Patients were asked in the survey to report on their perceived risk using words (measures used in the analysis) and in numbers on a scale of 0–100%, using the question "At that time, on a range of 0% to 100%, what did you think was the percent chance of your breast cancer coming back in the next 10 years?" (Tzeng et al., 2010). We compare below the measures on the two scales, and justify the choice of the measure using words.

874 patients reported on their perception of the chance of recurrence at 10 years in words, and 844 also gave a response using numbers in the open-ended question asking for a value 0-100%. Using words, 25% of the women reported a very low chance, 34% a low chance, 30% a moderate chance, and 11% a high/very high chance (Table 2.3). The measures of perceived risk in words and in numbers were consistent and highly correlated (rho= .72, P< .0001), but the spread of the risk in numbers was wide for the highest risk categories (Figure 2.S1), suggesting that the agreement between women may be low on how a moderate-to-very high risk translates in numbers. We also compared the measures with the risk of recurrence predicted by the genomic test. The perceived risk in words was weakly and significantly correlated with the recurrence risk categories based on the test (rho= .1237, P < .002). The relationship between the RS and the perceived risk in numbers was even weaker (rho = .07, P= .044; Figure 2.S2). Still, the distributions of perceived risk in numbers were significantly different between the risk categories based on the genomic test (Figure 2.S3), suggesting that perceived risk and predicted risk were related. Again, the spread of the distributions was wide, and thereafter, we used only the perceived risk expressed in words for the analysis.

2.7.3 Supplemental Figures and Tables

Figure 2.S1: Comparison of patient perceived risk reported in words and in numbers

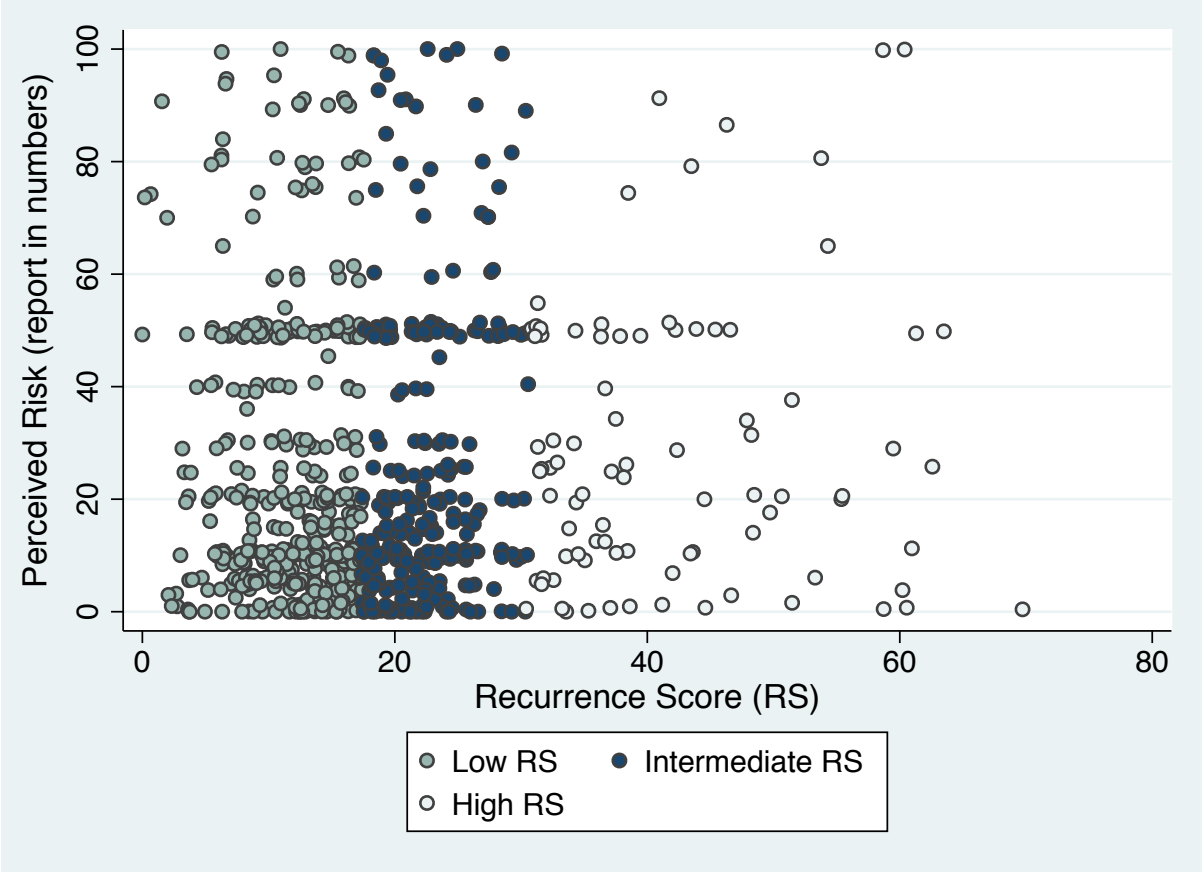


Box and whiskers plots for the distribution of perceived recurrence risk reported in numbers by categories of perceived risk reported in words. For each category, the box covers the 25th to 75th percentiles of the distribution, and the line within the box indicates the median; whisker ends show the most extreme values, or values within 1.5 interquartile of the quartile; outliers are indicated by dots.

The perceived risk of cancer recurrence at 10 years was measured in the survey in words (5 exclusive categories: *very low, low, moderate, high,* and *very high*) and in numbers (chance from 0 to 100%). The two categories, *high* and *very high* risk, were pooled together because of the small numbers of reports. Overall the distribution plot shows consistency between the patient reports in number and in words; significant variance of the risk expressed in number between the categories was observed using ANOVA ($P < .001$).

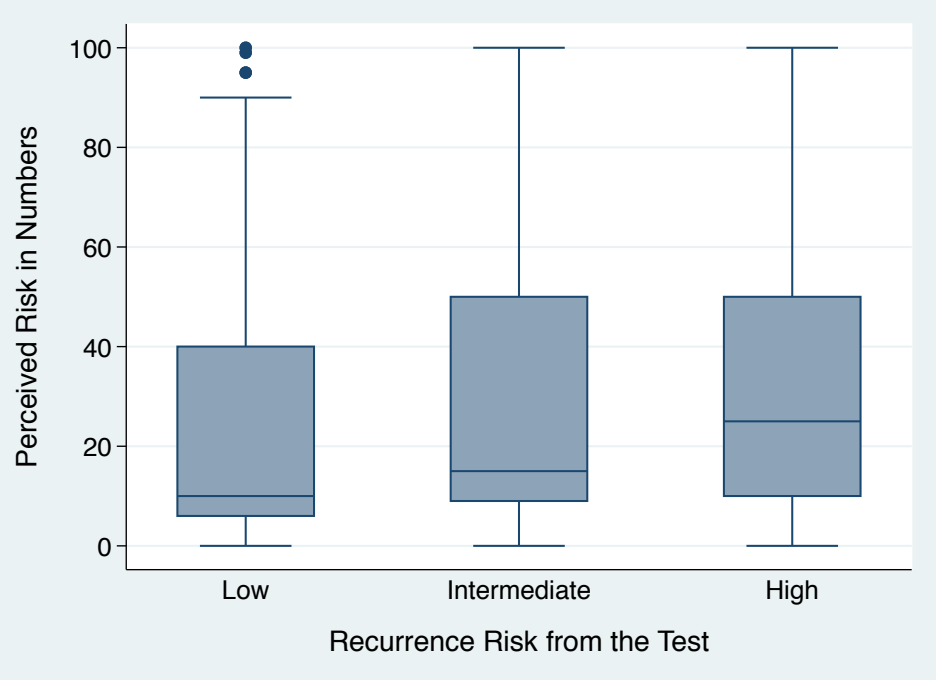
Of note, there was a significant bias towards the value 50% in the risk category “Moderate” (used by 102 out of 260 patients who reported perceiving a moderate risk).

Figure 2.S2: Comparison of the perceived recurrence risk in numbers and the recurrence score



The perceived risk reported by individual participants in numbers was plotted against the recurrence score (RS) from the laboratory test. The colors of the markers indicate the risk classification of each patient based on the test (grey: low, or RS<18; dark: intermediate, or RS 18–30; white: high, or RS>30). The data was slightly jittered to show overlapping points.
The pattern observed is consistent with the weak correlation of the two measures (rho =.07; P=.044).

Figure 2.S3: Distribution of the numeric values for perceived risk by category of recurrence risk predicted by the genomic test



Perceived risk distributions are summarized using box-and-whisker plots in which the box covers the 25th to 75th percentiles for each category of recurrence risk predicted by the test (i.e., Low, Intermediate, or High), and the line within the box indicates the median; whisker ends show the most extreme values, or values within 1.5 interquartile of the quartile; outliers are indicated by dots.
The means of the numeric values for the perceived risk are significantly different between risk categories using ANOVA (overall F test and individual Wald tests for pair-wise comparisons of coefficients, all significant with P values < .05).

Table 2.S1: Comparison of the complete cases used in regression analyses and the cases with missing values

	Sample 1- Risk perception			Sample 2- Treatment decision		
Characteristics	**Complete cases N = 728**	**Cases with missing values n = 166**	**P**	**Complete cases n = 677**	**Cases with missing values n = 203**	**P**
Chemotherapy use	**241 (33%)**	**41 (25%)**	**.035**	**229 (34%)**	**53 (24%)**	**.009**
Recurrence risk			.937			.654
Low	401 (55%)	91 (55%)		367 (54%)	125 (58%)	
Intermediate	251 (34%)	59 (36%)		238 (35%)	72 (33%)	
High	76 (10%)	16 (10%)		72 (11%)	20 (9%)	
Chemotherapy preference			.922			.808
< 2y	151 (21%)	11 (22%)		138 (20%)	24 (24%)	
3–5 y	100 (14%)	8 (16%)		95 (14%)	13 (13%)	
6–10y	101 (14%)	6 (12%)		93 (14%)	14 (14%)	
> 10	290 (40%)	17 (35%)		272 (40%)	35 (35%)	
No years worth	86 (12%)	7 (14%)		79 (12%)	14 (14%)	
Perceived risk			.313			.146
Very Low	174 (24%)	47 (31%)		158 (23%)	63 (31%)	
Low	253 (35%)	50 (33%)		240 (35%)	63 (31%)	
Moderate	221 (30%)	39 (26%)		206 (30%)	54 (27%)	
High/Very high	80 (11%)	16 (11%)		73 (11%)	23 (11%)	
Age at test	51.9 (7.0)	52.7 (6.9)	.149	**51.7 (7.0)**	**53.1 (6.8)**	**.008**
Race/Ethnicity			**.012**			**<.001**
White	**460 (63%)**	**89 (55%)**		**429 (63%)**	**120 (56%)**	
Hispanic	89 (12%)	19 (12%)		89 (13%)	19 (9%)	
Black	**78 (11%)**	**34 (21%)**		**67 (10%)**	**45 (21%)**	
Asian	81 (11%)	16 (10%)		73 (11%)	24 (11%)	
Other	20 (3%)	4 (2%)		19 (3%)	5 (2%)	
Health			.187			.164
Excellent	148 (21%)	26 (16%)		135 (20%)	39 (19%)	
Very good	333 (47%)	68 (42%)		319 (47%)	82 (40%)	
Good	194 (27%)	54 (33%)		179 (26%)	69 (34%)	
Fair/poor	46 (6%)	14 (9%)		44 (7%)	16 (8%)	
SES						
≤ High school	89 (12%)	26 (15%)	.256	84 (12%)	31 (14%)	.502
Graduate school	**197 (28%)**	**21 (13%)**	**<.001**	187 (28%)	**31 (15%)**	**<.001**
Income < $40,000	**75 (10%)**	**30 (18%)**	**.006**	**68 (10%)**	**37 (17%)**	**.006**
Income ≥ $150,000	**211 (30%)**	**24 (17%)**	**.002**	**202 (31%)**	**33 (17%)**	**<.001**
Lower health literacy	4.3%	6.9%	.128	4.3%	5.7%	.388
Communication	.01 (.98)	-.04 (1.09)	.582	.00 (.99)	.00 (1.04)	.952
Physician mistrust	.02 (.99)	-.10 (1.07)	.196	.02 (.98)	-.08 (1.07)	.252
Family support	-.01 (1.01)	.05 (.93)	.523	.00 (1.00)	.00 (1.00)	.967
Time opportunity	-.03 (.99)	.15 (1.07)	.072	**-.03 (.98)**	**.17 (1.07)**	**.043**

	Sample 1- Risk perception			Sample 2- Treatment decision		
Characteristics	**Complete cases N = 728**	**Cases with missing values n = 166**	**P**	**Complete cases n = 677**	**Cases with missing values n = 203**	**P**
Worry about work	.01 (1.00)	-.05 (.95)	.582	.01 (1.00)	-.06	.468
Year of treatment			.269			.556
2009	95 913%)	20 (13%)		88 (13%)	27 (12%)	
2010	162 (22%)	35 (21%)		151 (22%)	46 (21%)	
2011	225 (31%)	42 (25%)		208 (31%)	59 (27%)	
2012	246 (34%)	69 (425)		230 (34%)	85 (39%)	
U.S. Census region			**.002**			**.001**
Northeast	**149 (20%)**	**56 (34%)**		**139 (21%)**	**66 (30%)**	
North Central	82 (11%)	18 (11%)		73 (11%)	27 (12%)	
South	358 (49%)	72 (43%)		328 (49%)	102 (47%)	
West	**139 (19%)**	**20 (12%)**		**137 (20%)**	**22 (10%)**	

P < .05 indicates a significant difference between complete cases and cases with missing values for one sample. Sample 1 was used to model the risk perception on patient preferences and other characteristics. Sample 2 was used to model the treatment decision on risk perception, patient preferences and other characteristics using the multivariate logistic model and the KHB method.

Table 2.S2: Odds ratio for the propensity to report higher risk perception based on patient factors

	Model 1		Model 2		Model 3	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Chemotherapy Preference						
< 2y (High preference)			0.63	[0.39,1.02]		
3–5 y (ref.)			1	-		
6–10y			**0.56***	**[0.33,0.96]**		
> 10 (Low Preference)			**0.43*****	**[0.26,0.71]**		
No years worth (Aversion)			**0.43***	**[0.23,0.82]**		
Low preference for chemotherapy					**0.69***	**[0.52,0.93]**
Patient characteristics						
Age at test (y) #	0.98	[0.79,1.21]	0.96	[0.77,1.18]	0.96	[0.78,1.19]
Squared value of age #	1	-	1	-	1	-
Race/Ethnicity						
White (ref.)	1	-	1	-	1	-
Hispanic	**1.49**	**[0.99,2.24]**	**1.69***	**[1.09,2.62]**	**1.53***	**[1.00,2.34]**
Black	0.62	[0.36,1.07]	0.76	[0.43,1.36]	0.68	[0.40,1.16]
Asian	0.78	[0.52,1.15]	0.88	[0.59,1.31]	0.8	[0.54,1.17]
Other	1.31	[0.52,3.29]	1.23	[0.49,3.08]	1.28	[0.50,3.29]
Socio-economic status						
≤ High school graduate	**2.07****	**[1.31,3.26]**	**2.13****	**[1.32,3.42]**	**2.00****	**[1.25,3.22]**
Income < $40,000	0.92	[0.57,1.47]	0.96	[0.61,1.49]	0.94	[0.59,1.50]
Lower health literacy	**0.42***	**[0.20,0.89]**	**0.45***	**[0.21,0.95]**	**0.42***	**[0.20,0.90]**
Communication, score	1	[0.86,1.16]	1.02	[0.88,1.18]	1.03	[0.88,1.20]
Physician mistrust, score	1.12	[0.93,1.34]	1.14	[0.94,1.38]	1.14	[0.95,1.36]
Year of treatment						
2009	0.66	[0.41,1.06]	0.67	[0.41,1.09]	0.68	[0.42,1.09]
2010	0.88	[0.61,1.27]	0.9	[0.63,1.29]	0.9	[0.63,1.29]
2011	0.92	[0.68,1.25]	0.94	[0.70,1.27]	0.93	[0.69,1.26]
2012 (ref.)	1	-	1	-	1	-
U.S. Census region						
Northeast (ref.)	1	-	1	-	1	-
North Central	0.81	[0.51,1.27]	0.73	[0.46,1.16]	0.74	[0.47,1.17]
South	0.86	[0.56,1.33]	0.83	[0.53,1.31]	0.83	[0.54,1.27]
West	0.67	[0.38,1.19]	0.62	[0.34,1.14]	0.65	[0.36,1.15]
Chi2	40.38		47.55		45.5	
AIC	1919.82		1911.75		1915.1	

* P<0.05, ** p<0.01, *** p<0.001

N= 728 complete cases. The base outcome is “very low” perceived risk, compared to low, moderate, and high/very high. Odds ratios are presented with 95% confidence intervals and significance of the P values for the individual Wald tests. The models were adjusted for patient clustering by areas of residence (cluster = 160 CBSA).

The logistic regression models were run on the same sample to test the significance of the association of chemotherapy preference and risk perception (comparing model 1 and model 2). We also tested the association of the propensity to report low preference for chemotherapy as a proxy measure for latent patient characteristics that may influence risk perception (model 3).

The assumption of proportional odds was verified on the corresponding ordered logistic model unadjusted for clustering. The assumption of proportional odds was tested using the Brant test that compares the coefficients obtained from an ordered logistic model with those obtained from the implied logistic models for each of the independent variables. # Both age and its square value were included in the model to accommodate the assumption of proportional odds. Age is collected from claims; other data are from self-reports.

Table 2.S3: Association of patient preferences and risk perception with chemotherapy use

Chemotherapy Use	Model 1 - Base		Model 2- Risk Perception		Model 3- Low Preference		Model 4- Full Model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Perceived risk								
Very low			1	-			1	-
Low			1.47	[0.82,2.64]			1.47	[0.82,2.63]
Moderate			1.77	[0.90,3.50]			1.83	[0.91,3.67]
High/Very High			**2.83***	[1.34,5.99]			**3.09***	[1.48,6.48]
Low preference					**1.71***	[1.10,2.65]	**1.83***	[1.19,2.81]
Age	**0.95***	[0.92,0.99]	**0.95***	[0.92,0.99]	**0.95***	[0.92,0.99]	**0.95***	[0.91,0.99]
Recurrence risk								
Low (ref.)	1	-	1	-	1	-	1	-
Intermediate	**12.73****	[7.40,21.88]	**12.74****	[7.52,21.59]	**13.13****	[7.57,22.77]	**13.17****	[7.67,22.61]
High	**113.80****	[45.5,284.7]	**109.34****	[43.9,272.7]	**118.24****	[46.2,302.8]	**112.95****	[44.2,288.7]
Health								
Excellent (ref.)	1	-	1	-	1	-	1	-
Very good	0.87	[0.49,1.57]	0.82	[0.45,1.50]	0.87	[0.49,1.54]	0.82	[0.45,1.48]
Good	1	[0.41,2.39]	0.94	[0.39,2.26]	0.98	[0.41,2.38]	0.92	[0.38,2.25]
Fair/Poor	2.09	[0.80,5.47]	1.9	[0.74,4.92]	2	[0.77,5.22]	1.84	[0.71,4.74]
Race/Ethnicity								
White (ref.)	1	-	1	-	1	-	1	-
Hispanic	1.65	[0.96,2.84]	1.57	[0.89,2.75]	1.64	[0.95,2.83]	1.54	[0.88,2.72]
Black	2.03	[0.77,5.35]	2.18	[0.81,5.88]	1.82	[0.66,5.07]	1.93	[0.68,5.52]
Asian	0.84	[0.41,1.74]	0.87	[0.42,1.78]	0.84	[0.41,1.71]	0.87	[0.43,1.76]
Other	0.63	[0.16,2.44]	0.6	[0.15,2.34]	0.62	[0.17,2.34]	0.58	[0.15,2.20]
SES								
≤ High school grad.	1.15	[0.58,2.26]	1.05	[0.53,2.10]	1.25	[0.62,2.49]	1.14	[0.56,2.33]
Income < $40,000	0.55	[0.27,1.11]	0.54	[0.26,1.13]	0.52	[0.26,1.05]	0.5	[0.24,1.06]
Low health literacy	0.77	[0.31,1.95]	0.89	[0.34,2.37]	0.78	[0.31,1.95]	0.91	[0.35,2.37]
Communication	**0.75**	[0.56,1.00]	**0.75**	[0.55,1.02]	**0.71***	[0.53,0.96]	**0.71***	[0.52,0.97]
Physician mistrust	0.82	[0.62,1.09]	0.81	[0.60,1.10]	0.8	[0.60,1.07]	0.79	[0.59,1.07]
Family support	1.14	[0.97,1.35]	1.14	[0.96,1.36]	1.13	[0.95,1.34]	1.13	[0.94,1.35]
Opportunity cost	**0.71***	[0.56,0.91]	**0.71***	[0.56,0.89]	**0.67***	[0.52,0.86]	**0.66***	[0.52,0.84]
Worry about work	1	[0.81,1.24]	1	[0.80,1.25]	1.01	[0.81,1.26]	1.01	[0.81,1.26]
Health plan type								
Point-Of-Service	1	-	1	-	1	-	1	-
PPO/Indemnity	0.78	[0.35,1.71]	0.78	[0.35,1.72]	0.79	[0.35,1.79]	0.79	[0.35,1.79]
HMO	0.62	[0.24,1.57]	0.63	[0.24,1.64]	0.64	[0.26,1.56]	0.66	[0.26,1.63]

Continued on next page

Chemotherapy Use	Model 1 - Base		Model 2- Risk Perception		Model 3- Low Preference		Model 4- Full Model	
Year of treatment								
2009	1.33	[0.60,2.95]	1.26	[0.55,2.85]	1.35	[0.59,3.07]	1.28	[0.55,2.99]
2010	1.46	[0.75,2.82]	1.37	[0.68,2.77]	1.45	[0.73,2.87]	1.37	[0.67,2.84]
2011	1.11	[0.59,2.07]	0.99	[0.51,1.91]	1.13	[0.59,2.15]	1.02	[0.52,2.00]
2012 (ref.)	1	-	1	-	1	-	1	-
U.S. region								
Northeast (ref.)	1	-	1	-	1	-	1	-
North Central	0.69	[0.34,1.41]	0.72	[0.36,1.43]	0.78	[0.38,1.58]	0.82	[0.41,1.64]
South	0.61	[0.36,1.04]	0.62	[0.36,1.04]	0.64	[0.38,1.08]	0.65	[0.39,1.09]
West	0.8	[0.42,1.52]	0.85	[0.46,1.59]	0.81	[0.43,1.54]	0.87	[0.47,1.62]
Chi-2	271.25		282.27		250.41		257.71	
AIC	618.96		617.52		615.53		612.85	

* P<0.05, ** p<0.001. N=677 complete cases in 152 CBSA.
The table presents odds ratios, 95% confidence intervals and P-value for a series of logistic models including patient characteristics (Model 1); and perceived risk of recurrence (Model 2), propensity for low chemotherapy preference (Model 3), or both (Model 4). All models are controlled for age, factors that may affect the decision of receiving chemotherapy, year of testing, and U.S. regions, with clustering adjustment by areas of residence (clusters= 152 CBSA). Recurrence risk is the category of risk predicted by the genomic test (laboratory records). Age was collected in claims data. Other data are self-reports from the survey.

CHAPTER 3

INTERACTION OF INFORMATION EXCHANGE AND RISK PERCEPTION ON THE TREATMENT DECISION

3.1 ABSTRACT

Purpose

Genomic tests predicting tumor recurrence risk may help inform treatment decisions and improve quality of care. Yet differences in information exchange and patient decision style about genomic tests may further exacerbate disparities in care, particularly if recommendations conflict with patients' preferences or other prognostic information.

Patients and methods

We used a retrospective study design and multivariate analysis to look at the information exchange between patients and physicians in the context of receiving a genomic test for early-stage breast cancer. A mailed survey collected information on test knowledge, treatment experience, and decision style from a national sample of privately insured women aged less than 65, who received genomic testing for early-stage breast cancer in 2009–2012. Survey responses were linked to claims data and test results. We used multivariate logistic regression models to examine the association of patient demographics and decision style with the knowledge of the test result as a measure of information exchange. We also examined the interaction of information exchange and patient risk perception in a multivariate logistic regression analysis modeling the treatment decision. Models were adjusted for patient age, race/ethnicity, socio-economic status, quality of interaction with their physician, year of testing, and geographic clustering.

Results

Among the 896 respondents, most women reported active decision styles. Most patients heard about the genomic test from their physicians, and reported that their physician recommended the

test. Only 14% of the patients asked to be tested. Twenty percent of the patients did not know their recurrence risk category. Significant differences in knowledge were detected by race/ethnicity after controlling for age, education and income. A significant interaction of patient knowledge and risk perception was detected in a model for the chemotherapy decision.

Conclusion

While most women reported more active styles of decision-making, we found significant differences in information exchange that may influence the treatment decision. Variations in patient reports may reflect variation in understanding and retaining information about the genomic test, or in information delivery by physicians.

3.2 INTRODUCTION

The patient-centered approach to cancer care emphasizes the involvement of the patient in the treatment decision (Epstein and Street, 2007; Institute of Medicine, 2013). Indeed, there is strong evidence that a more active decision style (with the decision being either shared between physician and patient, or patient-controlled) is associated with greater patient satisfaction and often better health outcomes (Brown et al., 2012). As a correlate, a passive (or physician-based) decision style was associated with lower patient satisfaction and lower quality of life (Andersen et al., 2009). Shared decision-making more specifically applies when a choice between several treatment options is sensitive to patient preferences. This approach recommends that physicians elicit patient preferences and incorporate them in the decision, together with clinical factors (Politi and Street, 2011).

Effective communication is a central element to achieve shared decision-making, and patients should be presented with sufficient information to balance the risks and benefits of different treatment options (Epstein and Street, 2007). In addition to communication itself, the Framework for Patient-Centered Communication identifies patient characteristics and components of the patient-physician interaction as moderators and mediators for the effect of communication on health outcomes (Epstein and Street, 2007). In this framework, health literacy (i.e., understanding health information, but also knowing when and where to seek it) is an important patient characteristic to sustain effective communication about the treatment (Institute of Medicine, 2004), and low health literacy may constitute a barrier to the patient's involvement in the decision. Patient education and health literacy may also influence both assertiveness and information retention. As the discussion about the treatment decision begins, patients who are more activated (i.e., who combine knowledge, skills and confidence to manage their health condition) may show more self-advocacy, express their opinions and preferences more actively,

and feel empowered to ask for additional information (Politi and Street, 2011). Provider characteristics are also important in this process; in particular, the cultural competence of the provider may facilitate the process of eliciting patient preferences, and help attain a decision better suited for the patient (Wang et al., 2013). Not only may patient preferences translate into differences in willingness to undergo treatment (Brewer et al., 2009a; Duric et al., 2005; Hamelinck et al., 2014; McQuellon et al., 1995), but they may also influence the acceptance of a treatment option by attenuating or accentuating its perceived risks and benefits (Epstein and Street, 2007). Patient trust in the physician and perception of good communication are also crucial elements of decision-making as they are likely to promote patient engagement, and increase the likelihood that a patient follows the recommendation of the physician (Mandelblatt et al., 2012; Mandelblatt et al., 2010; Mojica et al., 2007b).

Finally, decision style is an important factor in shaping patient involvement in the decision-making. It is now well documented that most patients are willing to participate in treatment decisions and express a preference for being active during decision-making (Defrank et al., 2013a; Degner et al., 1997a; Hawley et al., 2007; Hawley et al., 2008; Janz et al., 2004; Katz et al., 2005; Lo et al., 2010). But patient preferences may also shape the mode of decision-making, and being actively involved may not be desired or valued by all patients (Degner et al., 1997a; Livaudais et al., 2013). For instance, patients preferring to rely on physician expertise may feel confused if they are asked to participate in the treatment decision (Harder et al., 2013). These observations underscore the need to assess patient preferences early on during the discussion about treatment decision.

A patient's desire to be more involved in decision-making may be difficult to satisfy during the traditional patient-physician encounter, in part due to insufficient time for information

exchange (Degner et al., 1997a; Ravdin et al., 1998; Siminoff et al., 2006). For instance, a study of women diagnosed with early-stage breast cancer in 2001-2003 found overall low levels of knowledge about the outcomes of surgery options (Fagerlin et al., 2006). Only half of the patients knew that mastectomy and breast-conserving surgery resulted in same survival rate and only 16% knew about differences in recurrence. In this sample, African American women presented lower level of knowledge than Whites (Fagerlin et al., 2006). Remedying gaps in patient knowledge is important not only to make an informed decision, but also because some patients may value receiving information more than their active involvement in the decision (Chung et al., 2012; Smith et al., 2009).

Furthermore, the quality of the information exchange was found to interact with the decision style during the treatment decision. While evidence supports the positive impact of a decision shared by patient and physician, there is a risk that a fully active (autonomous) decision style may lead to decisions discordant with treatment guidelines if a patient is not "well informed" (Katz and Hawley, 2007; Katz et al., 2005). Nonetheless those preferences may be mutable, and receiving appropriate information may lead to a change in decision by overcoming patients' subjective preferences (Katz et al., 2010).

Since 2007 clinical guidelines for the care of early-stage breast cancer recommend the use of a genomic test to guide the decision of adding chemotherapy to the treatment of estrogen receptor –positive (ER+), lymph node–negative (LN–) breast cancer (Harris et al., 2007; NCCN, 2008). In practice, the use of the test has led to a 24%–44% decrease in the use of chemotherapy (Ademuyiwa et al., 2011; Asad et al., 2008; Henry et al., 2009; Holt et al., 2013; Lo et al., 2010; Rayhanabad et al., 2008). While the test produces an objective measure of the recurrence risk,

the treatment decision may be difficult if the test recommendation conflicts with patient preferences. Early surveys of breast cancer survivors documented a strong interest in genomic testing and a desire for knowledge about the test (Lipkus et al., 2011; O'Neill et al., 2007). Patients receiving the test during their treatment reported satisfaction with being tested, despite a potential increase in worry (Lo et al., 2010). Yet, another study pointed to significant gaps in knowledge and understanding of the genomic test, with 30% of the patients surveyed not fully understanding the test result (Tzeng et al., 2010). Also, several studies documented an overall low level of information retention about the test significance among patients receiving the test (Lillie et al., 2007; Richman et al., 2011; Seror et al., 2013). Knowledge about the test was found to vary significantly with patient characteristics, including education, numeracy, and decision style (Richman et al., 2011). More specifically, women at intermediate risk who favored a passive decision style reported higher cancer-related distress and poorer quality of life, and the effect tended to be worse for White women compared to Hispanic and Black women (Sulayman et al., 2012). While those studies bring important insights on patient's processing of information related to genomic testing, the body of evidence is very fragmented coming mostly from small studies with predominantly White participants (Lipkus et al., 2001; Richman et al., 2011; Tzeng et al., 2010). This lack of participant diversity may hinder the identification of issues specific to minority patients.

There is no convincing evidence for a direct association of race/ethnicity with decision style (Garfield et al., 2007; Hubbard et al., 2008; Say et al., 2006), but variations in decision style are strongly associated with patient characteristics such as age, education, and income that are often correlated with race/ethnicity (Hubbard et al., 2008; Mandelblatt et al., 2012; Peek et al., 2011). In addition to education, health literacy may affect decision making, with women at higher levels

of health literacy perceiving more accurately their recurrence risk and valuing more information from new technologies, such as personalized medicine. Among minority patients, these issues have been identified as major sources of disparities in receiving quality health care in general and in shaping attitudes towards genetic testing and therapeutic decisions in particular (Allford et al., 2013). There is also evidence that initiation of the information exchange during the medical encounter may be more difficult for minority patients who may be less likely to ask questions and to benefit from the support of a companion during their visits (Eggly et al., 2011; Greenberg et al., 2011).

To fill this gap in knowledge on the preferences and attitudes of more diverse patient populations regarding the use of the genomic test in treatment decision, we used data from the ECHO study, or "*Empowering CHOices for Breast Cancer Treatment*." ECHO included a national survey of non-elderly, privately insured women treated for hormone receptor positive, lymph node negative (ER+ LN–) breast cancer in 2009-2012, with a large representation of minority women (35%). All the patients had received the genomic test during their treatment, and we found that in this cohort the test result was a strong determinant for the use of chemotherapy (Chapter 2). Guided by the Health Behavior Framework (Bastani et al., 2010), and by the Model for Patient-Centered Communication in Cancer Care (Epstein and Street, 2007), we previously examined patient characteristics that may influence the treatment decision of using chemotherapy in the context of the genomic test. In particular, we found that patient risk perception intervened between patient preferences for chemotherapy and treatment decision (Chapter 2). In the present study, we aimed to elucidate another pathway potentially affecting the treatment decision. We looked at patient reports about the *information exchange* with physician with the hypotheses that variations in information exchange were associated with race/ethnicity

and other patient characteristics, that there was a significant relationship of *information exchange* with the *treatment decision* to receive chemotherapy, and that *risk perception* moderated this relationship.

3.3 METHODS

3.3.1 Data Source, Population and Data Collection

Data source, patient population and data collection are described in Chapter 1, Section 1.4. Briefly, this retrospective study combines data from a patient survey linked to claims information and laboratory records for the genomic test. Women younger than 65 years, who had received the most common, commercial genomic test for early-stage breast cancer between January 2009 and November 2012, were eligible for the study. The survey administered between August 2nd, 2013 and December 31st , 2013, resulted in a 63% response rate with 896 respondents.

3.3.2 Measures

Measures for the information exchange

The main measure for the *information exchange* is the patient knowledge of the test result as an outcome of this exchange. The patients were first asked if they had received the test during their treatment ("Yes"/"No"/"I don't know"), and if they had, they were asked for the risk predicted by the test with a choice of: "Low", "Intermediate", "High," and "I don't know." An indicator was generated for a patient *knowledge of the test result*, with value 1 if the patient had chosen "Low", "Intermediate", or "High"; and value 0 if the patient reported "I don't know", or if the patient selected "No" or "I don't know" at the previous question asking about receiving the test.

A second measure for the information exchange was the patient rating of the amount of information given by their physician about the clinical significance of the test—more specifically about "How the Onco*type* DX result might affect treatment recommendations," and about "How important the Onco*type* DX result is compared to other information (like tumor size) in measuring the chance of the cancer coming back," with the choice of answers "Not at all", "Too little", "About right", or "Too much." The items were modified from previous studies (Lillie et al., 2007; Ravdin et al., 1998). An indicator was built for receiving a "lower level of information" with the value 1 if a patient selected the answers "Not at all" or "Too little" for both items, and 0 otherwise.

Patients were also asked if they knew about the existence of a recurrence risk test at the time of diagnosis (yes/no), and from which source they had learned about it first, with item choices "Your doctor", "a relative", "a friend", "a coworker", "the media", "the internet", "social network media", "a cancer support group", or "other." Finally, patients were asked which statement applied best to their experience in considering the test between the three items: "I asked to receive the test", "My doctor recommended the test to me", and "I did not discuss the test with my doctor" (the respondents could select several items).

Patient characteristics

Age at the time of the test was collected from claims data. Race/ethnicity, health literacy, general health status, educational attainment, and annual household income were collected from the survey, as described in Chapter 2. Socioeconomic indicators used in the regression models included having an annual household income lower than $40,000, or greater than $150,000; and educational attainment equal to or lower than high school graduate, or at graduate school. Risk perception was measured by asking the participants about their personal perception of tumor

recurrence risk in the next 10 years, as described in Chapter 2. Recurrence risk based on the genomic test was collected from laboratory records. Information on adjuvant chemotherapy and radiation therapy was collected from claims. Patients were asked to report on the use of chemotherapy, radiation, and surgery type in the survey.

Patient-physician interaction

The quality of *patient-physician interaction* was assessed using a summary score for the quality of communication with the physician, with higher scores for greater quality of communication, and a summary score for physician mistrust, with greater score indicating greater mistrust, as described in Chapter 2.

Patient *decision style* concerning her breast cancer treatment was self-reported using a modified version of the 5-item Control Preference Scale (Degner et al., 1997a; Degner et al., 1997b). Response items were "I made my decisions with little or no input from my doctor", "I made my own decisions after seriously considering my doctor's opinion", "My doctor and I made the decision together", "I let the doctor make the decision but with serious consideration of my opinion", and "I left the decision to my doctor with little or no input from me." This scale developed by L.F. Degner and colleagues, is commonly used to measure the degree of involvement wanted and/or realized by breast cancer patients during cancer treatment (Degner et al., 1997a; Degner et al., 1997b; Hawley et al., 2007; Katz et al., 2005; Lillie et al., 2007). As commonly done, the responses were recoded into three decision styles: active, or patient-based (item 1 or 2); shared (item 3); and passive, or physician-based (items 4 or 5; Hawley et al., 2007; Kehl et al., 2015; Lillie et al., 2007). The 3-item categorical variable was used as a covariate in regression analysis, and individual indicators for the three decision styles were generated to examine the correlation with other covariates.

Other covariates

All models include a dummy variable for the year of testing, and take in account the clustering of patients by areas of residence (Core-based Statistical Areas from Census 2010, equivalent to metropolitan areas >10,000 residents) combined with a categorical variable for the four U.S. Census regions (Northeast, North Central, South, and West); both geographic information were collected from claims.

3.3.3 Statistical Analysis

Variable statistics are expressed as mean and standard deviation (SD) for continuous variables, and frequency for categorical variables, overall and after stratification by variables of interest. Differences in means and in distribution between groups were tested using two-sided t-test and analysis of variance (ANOVA), and Pearson's chi-square, respectively. Correlation between variables was tested by the significance of the pairwise correlation coefficients. Agreement between variables collected from different sources was measured as the observed percent agreement compared to the expected percent agreement that would be obtained by chance, and using Cohen's kappa statistics (Landis and Koch, 1977; Liu et al., 2010). Cohen's kappa indicates moderate agreement for values of 0.41–0.60; 0.61–0.80 indicate substantial agreement; and values over 0.80 show perfect agreement (Landis and Koch, 1977; Liu et al., 2010).

The association of information exchange with patient characteristics, including race and ethnicity, was examined using a multivariate logistic regression for the probability of a patient not knowing her recurrence risk, using the equation:

$$Y_{\text{Not Knowing Her Recurrence Risk}} = \beta_0 + \beta_1 * \text{Hispanic} + \beta_2 * \text{Black} + \beta_3 * \text{Asian} + \beta_4 * \text{Asian} + \Sigma (\beta_i * \text{covariate}) + \varepsilon$$

where $Y_{\text{Not Knowing Her Recurrence Risk}}$ is the log odds for the probability of a patient's lack of knowledge about the test result.

The association of information exchange with the treatment decision was tested using logistic regression for the probability of receiving chemotherapy based on the knowledge of the recurrence risk, risk perception and patient covariates, with and without an interaction term.

$$Y_{\text{Chemotherapy use}} = \beta_0 + \beta_1 * \text{“knowledge”} + \beta_2 * \text{“risk perception”} + \Sigma\,(\beta_i * \text{covariate}) + \varepsilon$$

$$Y_{\text{Chemotherapy use}} = \beta'_0 + \beta'_1 * \text{“knowledge”} + \beta'_2 * \text{“risk perception”} + \beta'_3 * \text{“risk perception”} * \text{“knowledge”} + \Sigma\,(\beta'i * \text{covariate}) + \varepsilon'$$

where $Y_{\text{Chemotherapy use}}$ is the log odds for the probability of receiving chemotherapy.

The hypothesis of an interaction between risk perception and information exchange was tested using the Wald test for the coefficient β'3 of the interaction term. As sensitivity analyses we examined the improvement of the model including risk perception and information after the addition of race/ethnicity, and after the addition of the recurrence risk predicted by the test. Differences in fit between nested models were tested using the log likelihood ratio test, with a significant result indicating a better model in presence of the new variable. Logistic models were evaluated using the Hosmer-Lemeshow goodness-of-fit test, and by measuring the area under the curve. Variances of predictive margins effects were estimated using Taylor Series approximation, with adjustment for multiple comparisons using the Bonferroni method when applicable. As alternative models, multilevel logistic regression models were considered and rejected because of the very small fraction of the variance explained by geographic clustering by CBSA and region (< 2%).

Less than 7% of the values were missing for any covariate, and all analyses were performed on complete cases (Table 3.S1). To test for potential selection bias, the characteristics of the complete cases were compared with those of the missing cases, and the only significant difference was observed for the knowledge of the recurrence risk: 81% of the complete cases knew their recurrence risk compared to 71% of the cases with missing values. If this selection caused a biased estimate for the effect of knowledge, it is likely a bias towards zero with an underestimation of the effect (Table 3.S1). Multivariate models were adjusted for patient age, race/ethnicity, education, health literacy, income; year of testing; U.S. Census region; and for clustering by area of residence (CBSA). Models for the probability of knowing the test result were also controlled for health, health literacy, decision style, good communication with the physician, and physician mistrust. Throughout the study, values are significant for P-value lower than 0.05. All analyses were performed using STATA 13 (Stata Corp., College Station, TX).

3.4 RESULTS

3.4.1 Patient characteristics

Demographic and clinical characteristics of the respondents are presented in Table 2.1 (Chapter 2). Based on laboratory results, 55% of the patients were predicted to be at low recurrence risk, 35% at intermediate risk, and 10% at high risk (Table 2.1).

The patient decision style during breast cancer treatment was reported to be active (or patient-based) by 47% of respondents, shared for 40%, and passive (or physician–based) for 13% (Table 3.S2). More active decision styles were reported by women who were younger, or at higher socio-economic status (SES), whereas higher rates of passive style were observed for women who were older, or at lower SES (Table 3.S2). No significant differences in decision

style were observed by race/ethnicity, or by health literacy. Reports of an active decision style were negatively correlated with good communication and positively correlated with mistrust (Table 3.1, both P <. 001). Inversely, the shared decision style was positively correlated with good communication and negatively with mistrust (Table 3.1, both P <. 001). There was no correlation of the passive decision style with either good communication, or mistrust (Table 3.1, both P > .255).

3.4.2 Patient knowledge about their treatment

33% of the women (n= 296) reported that they had received chemotherapy, and 31% of the women (n= 282) received chemotherapy according to the claims records. Agreement between patient reports and claims data was measured as the proportion of concordant reports and as Kappa statistics. A very high proportion of women (96%) reported correctly whether they had received chemotherapy or not, with almost perfect agreement (Kappa=0.93; 95% CI [0.86, 0.99]). The agreement was substantial for reports on radiation therapy, with 87% of concordant reports (Kappa=0.69; 95% CI [0.63, 0.76]). All women reported undergoing surgery (consistent with the test being performed on tumor tissue collected during surgery), but claims information on surgery procedures was missing for 19% of the respondents (n=169). So we examined instead the agreement of reports on breast-conserving surgery and on radiation therapy (that is recommended by the guidelines following this type of surgery). 530 participants reported breast-conserving surgery, and 82% of them reported being treated with radiation therapy, resulting in a 95% agreement between the two reports (Kappa=0.88; 95% CI [0.82, 0.95]). In conclusion, the survey reports show an overall high retention of information about medical procedures received during the breast cancer treatment in this cohort.

Patients were also asked to report on the results of the genomic test. 714 respondents (80%) indicated a risk category: low (53%), intermediate (21%) and high (6%; Table 3.2). The agreement between reported risk and laboratory records was substantial (82% agreement; Kappa =0.66, 95% CI [0.60, 0.72]). Only 14% of those 714 respondents reported a risk lower than it really was, and 2% overestimated their risk (Table 3.2).

20% of the respondents did not know their recurrence risk, and half of them (n= 87) were not aware that they had received the test during their treatment (38 women responded that they did not receive the test, and 49 did not know if they had). Knowledge of the test result varied significantly by race/ethnicity and SES. Women who did not know their result were significantly more often Hispanic (34%) or Black (32%) than White (15%) or Asian (17%; $P < .001$; Table 3.3), and had lower SES and lower health literacy than women who knew they were tested (39% of the patients reporting low income vs. 18% for higher income; 42% of patients at education level at high school or less vs. 17% for higher education level; 41% for patients at lower health literacy vs. 19% for those at higher level; all $P < .001$). We further examined the effect of race/ethnicity and other patient characteristics on the lack of knowledge of the test result using logistic regression (Table 3.4). Patient characteristics significantly associated with variations in knowledge, included race/ethnicity, poorer health, and lower education. Decision style was not significantly associated to patient knowledge in this model. Controlling for demographics, health, decision style and communication with the physician, the probability of not knowing her recurrence risk was on average 12 percentage points more for Hispanic women and 15 percentage points more for Black women than for White women of similar characteristics ($P \leq .001$). As expected, in this model the year of testing was also significant, suggesting a substantial loss in recall with time (Table 3.4).

While significant variations in knowledge were associated with patient demographics, the proportion of women who did not know their risk was not significantly different between the three risk categories based on the test result (average 20%, P= .135; Table 3.2). In contrast, among the women who reported a recurrence risk, reporting the same risk category as the laboratory records varied significantly by risk of recurrence (Table 3.2). 81% of the women at low risk reported correctly that they were at low risk, whereas only 52% of the intermediate-risk patients and 47% of the high-risk patients reported the correct risk category. As indicated above, women who reported an incorrect risk tended to report a risk lower that it actually was (Table 3.2). Those results show that patients in this cohort tend to retain accurate information, but also that variations existed by patient characteristics and by actual recurrence risk. We wanted to know if those differences in knowledge were linked to differences in content of the information, or in differences in amount of information exchanged. We first examined the sources of information reported by the patients in the survey.

3.4.3 Patient learning about the existence of the test and doctor recommendation

Physicians were the main source of information about the test existence for the participants. 638 participants (75%) reported knowing about the existence of this type of test at the time of diagnosis, but 60% of them (n=544) reported learning about it from their doctor first; only 11% of the patients reported learning about it from another source (most frequently friends or the Internet, each < 4%).

Most women (n=778, 87%) reported that the doctor recommended the test, and only 14% of the women (n=114) reported asking for the test (Table 3.3). A patient's report of a doctor

recommendation for the test was significantly associated with higher rate of knowledge about the test result (85% in case of a recommendation, vs. 47% if no recommendation; P < .001). Reports of doctor recommendation were less frequent among Hispanic and Black women (82% and 83%, respectively, vs. 89% for Whites and 91% for Asians; P= .007). Lower rates of recommendation were also observed among women at lower education level (75% vs. 89% for higher education level, P< .001), but no significant variations were detected by income, quality of communication, or mistrust. Of note, the rate of doctor recommendation was not associated with the year of testing, the laboratory result, or the chemotherapy use.

A lower proportion of patients reported asking for the test (14%, n=124), and most of them (54%) had learned about the test from a source other than their physician. Asking for the test was positively correlated with an active decision style and negatively correlated with a passive decision style (Table 3.1, both P< .05).

3.4.4 Patient rating of the information received about the test

Patient rating of the amount information given by the physician on the clinical significance of the test result was overall very good (Table 3.3). But significant differences were observed by race/ethnicity, with Black women more often reporting low level of information (Table 3.3). Proportions of reports for low level of information were also significantly different by education and income (19% for low income vs. 7% for higher income, P <. 001; 18% for lower education vs. 7% for higher education, P <. 001). Reporting a lower amount of information was correlated with physician mistrust and negatively correlated with good communication (Table 3.1, both P <. 001). Finally, the reports of lower amount of information were strongly correlated with the knowledge of the test result (Table 3.1, P <. 001).

3.4.5 Interaction between information exchange and risk perception on the treatment decision

Previously, we reported that risk perception was significantly associated with the treatment decision, with a higher likelihood of receiving chemotherapy among women perceiving a higher risk of recurrence (Chapter 2). We hypothesized that information exchange—measured here as the knowledge of the test result—may moderate the effect of risk perception, as predicted by the conceptual framework for Patient-Centered Communication in Cancer Care (Epstein and Street, 2007). We tested this hypothesis using a multivariate logistic regression modeling the probability of receiving chemotherapy in the presence of an interaction term between risk perception and knowledge of the test result (Table 3.5). In Model 1, both higher risk perception and lack of knowledge of the test result were associated with increased odds of receiving chemotherapy; in Model 2, the coefficients for the interaction term between the two covariates were significant for the two higher levels of perceived risk (moderate and high/very high risk; Table 3.5). The significance of the interaction term supported a moderation effect of risk perception on the effect of patient knowledge. Based on model 2, if a patient did not know her test result, the probability of receiving chemotherapy was increased on average by 10 percentage points, and by 25 percentage points for a patient perceiving low risk, controlling for other factors (Table 3.S3, both $P < .05$). We performed two sensitivity analyses to look for the effect of other factors that might influence the decision. First, the addition of race/ethnicity in the model (Table 3.5, Model 3) eliminated the effect of knowledge, but did not affect the effect of risk perception; this result is consistent with the strong association found between race/ethnicity and knowledge of the test result (Table 3.5). Second, adding the risk category based on the test improved significantly the model as shown by the significant log likelihood ratio test (Table 3.5, Model 4; Akaike, 1974).

As expected the risk of recurrence predicted by the test was the strongest determinant of chemotherapy in this model, and was dominant over patient knowledge; still, risk perception remained significant in the model consistent with the results presented in Chapter 2.

3.5 DISCUSSION

In a national sample of privately insured patients, aged less than 65, receiving genomic testing for their breast cancer treatment we found an overall high level of patient knowledge about the treatment that they received, and about their genomic test result. Still, significant variations in knowledge and information exchange were found in association with patient race/ethnicity, education, and quality of communication with their physician. In particular, Black and Hispanic women were significantly less likely to know the test result compared to White women after controlling for education, communication, and year of testing. Black women were also more likely to report receipt of low amounts of information about the test significance, compared to the other racial/ethnic groups.

Physicians were the main source of information about the test existence for this cohort, and receiving a recommendation for the test from the physician was strongly associated with better knowledge of the test result. The rate of doctor recommendation was significantly lower among Hispanic and Black patients compared to Whites and Asians. Finally, we found a significant interaction of risk perception and information exchange on the treatment decision (Table 3.5). This model supports that a patient perceiving lower risk of recurrence and who had knowledge of the result of the test was less likely to receive chemotherapy compared to a patient perceiving the same risk level but who did not know the test result (Table 3.5, Model 1). Also, the effect of not knowing the test result was weaker for patients perceiving higher risk compared to patients perceiving lower risk, as the addition of the interaction term in the model attenuated both the

effect of risk perception and the effect of the lack of knowledge (Table 3.5, Model 2). The effect of the patient knowledge became insignificant in the model in presence of the recurrence risk based on the test, and the effect of patient risk perception was slightly lower, consistent with the use of the genomic test to guide the treatment decision (Table 3.5, Model 4).

The retention of information on the genomic test result was high in this cohort of patients, with a recall time up to four years, which may relate to the overall high socioeconomic status. It is comparable to the 70% recall rate observed in a smaller study by Tzeng and colleagues (2010). Another study had found a much lower recall rate of 33%, using an open-ended question asking for the test result (Seror et al., 2013). As expected the knowledge of the test result was associated with education and health literacy, and also with the quality of communication with the physician. We found that information retention, that may reflect a more effective information exchange, was higher for women at low risk of recurrence compared to women at intermediate or high risk. Those differences will need to be further explored from the perspective of the physicians to determine if it relates to differences about the quality of the communication, or about the type of information given. It is possible that physicians may put more emphasis on test results indicating a low recurrence risk to explain why the treatment plan does not include chemotherapy. It is also possible that a physician may feel more comfortable communicating about a result with less uncertainty (compared to an intermediate-risk result), or about a more favorable prognosis (compared to a high-risk result). It is also possible that a patient is more likely to retain information of the test if it indicates a better prognosis.

Our findings highlight the essential role of the physician as the principal source of information about the test. We also found that a doctor's recommendation for the test was associated with better information exchange. It is possible that doctors who are more familiar

with the use of the test are both more effective in communicating about it, and also more likely to recommend it to the patients. The importance of achieving an effective information exchange is possibly amplified by the predominance of more active decision styles in this cohort. Notably and compared to studies of surgery decision in breast cancer treatment (Hawley et al., 2007; Katz and Hawley, 2007), the number of patients reporting a passive decision style was low—for instance, 13% in the present study vs. 22% in Hawley et al. (2007). Reporting a passive decision style was correlated to receiving lower amount of information about the test (Table 3.1), but also to lower odds of reporting a lack of knowledge of the test result (Table 3.4). These apparently contradictory observations may be explained by a lower activation of patients reporting a passive decision style. Patients who are less activated may receive information about the test result from the physicians, but may not feel empowered to ask for supplementary information.

Finally, we identified significant variations in information exchange associated with race/ethnicity, with Hispanic and Black women significantly more likely not to know their recurrence score after controlling for education and other patient characteristics. A passive decision style was more frequently reported by Hispanic women who were also the racial/ethnic group reporting the highest rate of receiving too much information about the test. In contrast, Black patients were more frequently reporting receiving too little amount of information. Those findings point to the need for interventions that may help support the information needs of specific patient subpopulations. Furthermore, we found previously that after controlling for other factors, Hispanic women were more likely to perceive elevated risk of recurrence, whereas Black women tended to underestimate the risk (Chapter 2). Variations in risk perception were also associated with lower education and lower health literacy that are strongly associated with race and ethnicity (Chapter 2). Our new findings of an interaction between risk perception and

information exchange calls for intervention that will support physician to elicit patient preferences and attitudes, and help in delivering information about the test result more efficiently. Previous studies have found that information is effective in changing patient subjective preferences and may help attain an informed treatment decision (Epstein and Street, 2007; Katz and Hawley, 2007).

A major strength of the study is the use of detailed material on treatment experience collected in a large and diverse population, and supported by the high agreement of the patient reports with objective data extracted from claims and laboratory results. In addition, the large size of the sample resulted in sufficient analytic power to look for patterns of care and patients perspective among different racial/ethnic groups. Our results help in identifying intervention targets that may be more specific to subpopulations of patients.

Still, our results need to be considered in the context of several limitations. First, a retrospective design and a large window of time (2009–2012) were necessary to ensure the recruitment of this diverse population. The resulting recall time (up to four years) may have affected the accuracy of patient reports. We attempted to control for the effect of time by including the year of treatment in all regression analyses, and found a significant effect of time on the knowledge about the test result.

There is the possibility of an omitted variable bias with the lack of information on tumor stage, tumor size and family history of cancer, that are likely to impact both the treatment decision and patient risk perception. Also, treatment experience may have tainted responses to questions probing the state of mind of the patient at the time of the decision. Furthermore, patient needs for information and preferences in decision-making may have changed over the course of the treatment, and such a retrospective report may reflect the perspective of the patient towards

the end of the treatment more than at the time of the decision (Vogel et al., 2008). It is also possible that an interaction of treatment experience with time resulted in differential recall. Some patients may tend to forget difficult experiences, while others may have a more vivid recollection of the event if the genomic test was perceived to have a positive impact on the treatment decision. This selective recall may explain in part why reports on the test result were more accurate among patients at low risk.

Time may present a second threat to internal validity due to changes in practice over time. It is likely that communication about the test and its result improves as a physician becomes more familiar with the test over time. There is also a higher probability that patients treated in the more recent years may have had more exposure to the test through experience of relatives and friends, although we did not find a significant difference in the patient's sources of information about the test between the years of testing.

We are missing information on the physician perspective: it is possible that a physician actually discussed the test and that the patient either did not retain the information at the time or forgot about it. It is even more likely among patients with lower education, as lower level of education was previously found to be associated with lower recall of information on genomic testing (Lillie et al., 2007). Unfortunately, the dataset does not include information from medical records that may indicate if the test was discussed during the visit. This asymmetry of information on what happened during the medical encounter may result in biased estimates due to the variables omitted in our model. However, even a patient's imperfect depiction of the information exchange may be relevant for the purpose of the study, as it may reflect on the long-term effects of the treatment on patients' satisfaction with the treatment decision and quality of life.

In conclusion, our study points to differences in information exchange that may lower the likelihood of informed decision-making. Differences in communication about the treatment decision are likely to impact patient satisfaction with care, and this effect may vary by race/ethnicity (Mojica et al., 2007b; Sulayman et al., 2012; Wildes et al., 2011).

Future studies should include a prospective design to document initial patient preferences in decision-making and knowledge, and determine how they may influence the treatment decision and long-term quality of life. Also it is essential to gain more insights on the physician perspective in the communication about the genomic test, and to identify mutable factors in the patient-physician encounter that may be targets for future interventions.

3.6 TABLES

Table 3.1: Pairwise correlations between patient-physician interaction, decision style and information exchange

	Good communication	Physician mistrust	Lower health literacy	Active decision style	Shared decision style	Passive decision style	No knowledge of test result	Lower amount of information
Physician mistrust	**-0.62 (0.000)**							
Lower health literacy	-0.05 (0.119)	**0.08 (0.019)**						
Active decision style	**-0.14 (0.000)**	**0.16 (0.000)**	0.02 (0.592)					
Shared decision style	**0.16 (0.000)**	**-0.19 (0.000)**	-0.04 (0.266)	**-0.77 (0.000)**				
Passive decision style	-0.03 (0.440)	0.04 (0.255)	0.03 (0.408)	**-0.36 (0.000)**	**-0.31 (0.000)**			
No knowledge of test result	0 (0.999)	0.02 (0.588)	**0.12 (0.000)**	-0.04 (0.202)	0.04 (0.225)	0 (0.900)		
Lower amount of information	**-0.12 (0.000)**	**0.15 (0.000)**	0.04 (0.252)	-0.02 (0.516)	-0.04 (0.197)	**0.1 (0.004)**	**0.33 (0.000)**	
Doctor recommendation	0.02 (0.473)	-0.05 (0.115)	-0.06 (0.085)	-0.06 (0.082)	**0.07 (0.028)**	-0.02 (0.527)	**-0.32 (0.000)**	**-0.37 (0.000)**
Patient asking for the test	0.03 (0.378)	-0.01 (0.838)	-0.06 (0.101)	**0.11 (0.001)**	-0.04 (0.223)	**-0.11 (0.002)**	**-0.13 (0.000)**	-0.06 (0.062)

Correlation coefficients, with P values in parentheses, for pairs of covariates based on patient reports on: quality of interaction with the physician (summary scores for higher quality of communication and greater physician mistrust), decision style (indicators for a report of active, shared, or passive decision style), measures of information exchange (indicators for a patient's lack of knowledge of the test result, for lower rating of the amount of information given by the doctor about the test significance, for a doctor recommendation of the test, and for a patient request for the test). Bold indicates significance at the 5% level.

Table 3.2: Comparison of patient reports and actual results collected from the laboratory

	Predicted Risk based on Test Results			
	Total	**Low risk** (n=492, 55%)	**Intermediate risk** (n=310, 35%)	**High risk** (n=92, 10%)
Patient Reports				
Low risk	470 (54%)	**387 (81%)**	75 (25%)	8 (9%)
Intermediate risk	190 (22%)	15 (3%)	**157 (52%)**	18 (20%)
High risk	54 (6%)	0	13 (4%)	**41 (47%)**
Did not know*	180 (20%)	90 (18%)	65 (21%)	25 (27%)

Frequency (percent by columns). Difference in distribution tested using Pearson's chi-square (P <. 001).

* Including respondents who reported that they were not tested, or did not know if they were tested

Table 3.3: Patient reports on information exchange about the test, overall and by race/ethnicity

Characteristic	All N = 896†	Hispanic n = 108 (12.1%)	Black n = 112 (12.6%)	Asian n = 97 (10.9%)	White n = 549 (61.7%)	Other[1] n = 24 (2.7%)	*P*
Patients reporting a risk category	715 (80%)	71 (66%)	76 (68%)	80 (82%)	468 (85%)	20 (83%)	**<.001**
Patients who did not know their risk*	181 (20%)	37 (34%)	36 (32%)	17 (17%)	81 (15%)	4 (17%)	
Patients unaware of being tested	87 (10%)	24 (22%)	17 (15%)	8 (9%)	35 (6%)	3 (13%)	**<.001**
Patient reporting the correct risk category	586 (65%)	52 (48%)	60 (54%)	69 (71%)	392 (71%)	13 (54%)	**<.001**
When considering the test:							
Doctor recommended the test‡	778 (87%)	88 (82%)	93 (83%)	88 (91%)	488 (89%)	16 (67%)	**.007**
Patient asked for the test‡	124 (14%)	14 (13%)	9 (8%)	11 (11%)	84 (15%)	5 (21%)	**.043**
Test was not discussed ‡	32 (4%)	9 (8%)	6 (5%)	1 (1%)	15 (3%)	1 (4%)	**.005**
Unknown	19 (2%)	2 (2%)	6 (5%)	3 (3%)	6 (1%)	2 (8%)	
Amount of information given about the test meaning							
Too little info /Not at all	72 (8%)	8 (7%)	15 (14%)	7 (8%)	41 (8%)	1 (5%)	**<.001**
About right	763 (86%)	82 (76%)	89 (79%)	81 (84%)	491 (89%)	5 (83%)	
Too much	24 (3%)	13 (12%)	1 (1%)	5 (5%)	4 (1%)	1 (4%)	
Missing	31 (3%)	5 (5%)	7 (6%)	4 (4%)	2 (8%)	-	

Frequency (percentage by column). Differences in distribution tested using Pearson's chi-square. Race/ethnicity is based on self-report and recoded as 5 exclusive categories; † race/ethnicity is unknown for 6 respondents [1] Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular. * Include those who did not know they were tested. ‡ Respondent could select more than one item.

Table 3.4: Odds ratios for the probability of a patient's lack of knowledge about the test result

Odds Ratios	OR	95% CI
Race/Ethnicity		
White (ref.)	1	-
Hispanic	**2.39*** **	**[1.48,3.88]**
Black	**2.85*** **	**[1.75,4.63]**
Asian	1.06	[0.46,2.43]
Other	0.87	[0.18,4.27]
Health		
Excellent (ref.)	1	-
Very good	0.84	[0.44,1.59]
Good	1.61	[0.87,2.97]
Fair/poor	**2.79***	**[1.25,6.22]**
Socio-economic status		
≤ High school graduate	**2.14****	**[1.29,3.55]**
Graduate school	**0.35*** **	**[0.20,0.62]**
Low income	1.78	[1.00,3.19]
High income	0.66	[0.36,1.23]
Decision style		
Active	1	-
Shared	1.1	[0.73,1.67]
Passive	0.52	[0.22,1.23]
Year of treatment		
2009	**3.57*** **	**[2.05,6.21]**
2010	**2.04****	**[1.20,3.47]**
2011	**1.79****	**[1.17,2.76]**
2012 (ref.)	1	-
U.S. Census region		
Northeast (ref.)	1	-
North Central	0.55	[0.29,1.02]
South	**0.56****	**[0.37,0.86]**
West	0.99	[0.56,1.76]
Chi2	187.12	
AIC	676.03	

* p<0.05, ** p<0.01, *** p<0.001

N = 771 complete cases in 165 CBSA. In addition the model was controlled for patient age, health literacy, good communication and physician mistrust who were found to be non-significant in the model and are omitted in the table presented here. The fit of the model was verified using the Hosmer-Lemeshow goodness-of-fit test. Area-under the curve is 0.78. Mean predicted probabilities of lacking knowledge of the test result with 95% CI: White: 15% [12%, 18%]; Hispanic: 27% [21%, 34%], Black: 30% [22%, 39%], Asian: 16% [7%, 25%].

Table 3.5: Odds ratios for the effect of risk perception and information exchange on the decision of receiving chemotherapy

Chemotherapy Use	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Perceived Risk								
Very low (ref.)	1	-	1	-	1	-	1	-
Low	1.51	[0.97,2.34]	1.51	[0.89,2.54]	**1.56***	**[1.00,2.44]**	**1.80***	**[1.13,2.86]**
Moderate	**2.15****	**[1.29,3.58]**	**2.77*****	**[1.58,4.85]**	**2.26****	**[1.35,3.78]**	**2.24***	**[1.21,4.15]**
High/very high	**3.54*****	**[2.00,6.26]**	**4.94*****	**[2.44,9.98]**	**3.69*****	**[2.05,6.64]**	**3.48*****	**[1.87,6.48]**
Knowledge of the test result								
Yes (ref.)	1	-	1	-	1	-	1	-
No	**1.56***	**[1.07,2.28]**	**2.60***	**[1.14,5.91]**	1.41	[0.96,2.08]	1.55	[0.91,2.63]
Risk x Knowledge								
Very low risk			1	-				
Low risk			1.16	[0.35,3.87]				
Moderate risk			**0.33***	**[0.14,0.81]**				
High/Very high risk			**0.23***	**[0.06,0.90]**				
Race/Ethnicity								
White (ref.)					1	-	1	-
Hispanic					1.49	[0.95,2.36]	1.63	[0.94,2.83]
Black					**2.03*****	**[1.46,2.83]**	1.95	[0.95,3.99]
Asian					0.93	[0.55,1.56]	0.92	[0.51,1.63]
Other					1.57	[0.57,4.29]	0.85	[0.24,3.10]
Risk from test result								
Low (ref.)							1	-
Intermediate							**16.50*****	**[10.26,26.52]**
High							**150.69*****	**[67.6,335.8]**
Age at test (y)	**0.97****	**[0.95,0.99]**	**0.97***	**[0.95,0.99]**	**0.97***	**[0.95,0.99]**	**0.96***	**[0.93,0.99]**
≤ High school graduate	0.96	[0.55,1.69]	0.93	[0.53,1.62]	0.99	[0.56,1.75]	0.89	[0.50,1.59]
Graduate school	1.15	[0.83,1.59]	1.19	[0.86,1.64]	1.1	[0.79,1.53]	1.2	[0.70,2.06]
Low income	0.73	[0.44,1.23]	0.77	[0.46,1.27]	0.67	[0.39,1.14]	**0.48***	**[0.26,0.90]**
High income	1.09	[0.76,1.58]	1.08	[0.74,1.58]	1.2	[0.82,1.76]	1.01	[0.61,1.67]
Year of treatment								
2009	1.25	[0.80,1.98]	1.17	[0.75,1.84]	1.32	[0.85,2.04]	0.92	[0.50,1.70]

2010	1.06	[0.76,1.48]	1.13	[0.82,1.55]	1.09	[0.78,1.51]	1.18	[0.74,1.86]
2011	1.38	[0.99,1.93]	1.38	[0.98,1.95]	**1.40***	**[1.00,1.95]**	1.46	[0.93,2.28]
2012 (ref.)	1	-	1	-	1	-	1	-
U.S. Census region								
Northeast (ref.)	1	-	1	-	1	-	1	-
North Central	**0.46***	**[0.24,0.89]**	0.47	[0.19,1.17]	1.33	[0.85,2.07]	1.28	[0.80,2.06]
South	**0.57***	**[0.36,0.89]**	0.71	[0.42,1.19]	0.97	[0.65,1.45]	1	[0.65,1.56]
West	0.94	[0.51,1.73]	1.1	[0.57,2.12]	1.03	[0.61,1.72]	1.06	[0.63,1.79]
Chi2	60.68		92.47		103.79		399.62	
Log likelihood	-491.8		-485.9		-486.5		-317.9	
AIC	1016		1010		1013		680	

* p<0.05, ** p<0.01, *** p<0.001 N= 820 complete cases in 168 clusters. Good fit of the models was verified using the Hosmer-Lemershow test for goodness of fit. Area under the curve: Model 1, 0.65; Model 2: 0.66; Model 3, 0.66; Model 4, 0.89. An increase in Chi2 or in log likelihood, or a decrease in Aikake Information Criteria (AIC) indicates that the model is improved with the addition of a covariate compared to the nested model that does include this covariate. The significance of the improvement was tested using a log likelihood ratio test: Model 2 vs. Model 1, Chi2(3, 11.69),) = .0085; Model 3 vs. Model 1, Chi2 (4, 10.54) P =. 0325; Model 4 vs. Model 3, Chi2 (2, 337.18) P <. 001.

3.7 SUPPLEMENTAL MATERIAL

Table 3.S1: Comparison of the characteristics of the whole cohort and sets of complete cases used in regression analysis

Characteristics	Sample 1- Knowledge			Sample 2- Treatment decision		
	Complete n=771	**Missing N= 123**	**P**	**Complete n=820**	**Missing n= 74**	**P**
Chemotherapy	248 (32%)	34 (28%)	.316	263 (32%)	74 (26%)	.257
Knowledge of test result	**626 (81%)**	**89 (71%)**	**.010**	**661 (81%)**	**54 (71%)**	**.047**
Age at test, mean y (SD)	51.8 (6.9)	53.5 (6.9)	.013	52.0 (7.0)	52.5 (6.9)	.522
Race/Ethnicity			.567			.938
White	480 (62%)	69 (58%)		506 (62%)	43 (61%)	
Hispanic	96 (13%)	12 (10%)		100 (12%)	8 (11%)	
Black	94 (12%)	18 (15%)		103 (13%)	9 (13%)	
Asian	80 (10%)	17 (15%)		90 (11%)	7 (10%)	
Other	21 (3%)	3 (3%)		21 (3%)	3 (4%)	
Health			.374			.697
Excellent	155 (20%)	19 (17%)		162 (20%)	12 (16%)	
Very good	355 (46%)	46 (41%)		366 (45%)	35 (47%)	
Good	209 (27%)	39 (35%)		228 (28%)	20 (27%)	
Fair/poor	52 (7%)	8 (75)		53 (7%)	7 (9%)	
SES						
≤ High school	93 (12%)	22 (18%)	.086	100 (12%)	15 (19%)	.060
Graduate school	204 (27%)	14 (12%)	.001	203 (25%)	15 (22%)	.576
Income < $40,000	92 (12%)	13 (10%)	.621	103 (13%)	2 (3%)	.010
Income ≥ $150,000	229 (30%)	6 (9%)	.001	232 (28%)	3 (20%)	.479
Lower health literacy	33 (4%)	8 (7%)	.211	38 (4.6%)	3 (4%)	.931
Communication	.00 (1.00)	-.02 (1.03)	.845	.00 (1.00)	-.02 (1.07)	.894
Physician mistrust	.01 (1.00)	-.11 (.95)	.269	.01 (1.00)	-.12 (.99)	.313
Decision style			.240			.587
Active	370 (48%)	46 (42%)		384 (48%)	32 (44%)	
Shared	308 (40%)	45 (41%)		324 (40%)	29 (40%)	
Passive	93 (12%)	19 (17%)		100 (12%)	12 (16%)	
Risk perception			.661			.933
Very low	193 (25%)	28 (24%)		208 (25%)	13 (22%)	
Low	265 (35%)	38 (32%)		281 (34%)	22 (37%)	
Moderate	292 (19%)	41 (34%)		242 (30%)	18 (30%)	
High/Very high	84 (11%)	12 (10%)		89 (11%)	7 (12%)	

Continued on next page

Characteristics	Sample 1- Knowledge			Sample 2- Treatment decision		
	Complete n=771	Missing N= 123	P	Complete n=820	Missing n= 74	P
Year of treatment			.417			.809
2009	102 (13%)	13 (11%)		107 (13%)	8 (115)	
2010	167 (22%)	30 (24%)		178 (22%)	19 (26%	
2011	236 (31%)	31 (25%)		244 (30%)	23 (31%)	
2012	266 (34%)	49 (40%)		291 (35%)	24 (32%)	
U.S. Census region			.052			.147
Northeast (ref.)	175 (23%)	30 (24%)		185 (22%)	20 (27%)	
North Central	84 (11%)	16 (13%)		87 (11%)	13 (18%)	
South	364 (47%)	66 (54%)		398 (49%)	32 (43%)	
West	148 (19%)	11 (9%)		150 (18%)	9 (12%)	

Model associated to Sample 1: Table 3.5; models associated to Sample 2: Tables 3.6 and 3.S4. The distribution by test result (low/intermediate/high risk) was not different between the groups.

Table 3.S2: Variations in patient-reported decision style by demographics

Decision Style	Active	Shared	Passive	*P*
Overall	**416 (47%)**	**353 (40%)**	**112 (13%)**	
Age				.025
< 50	115 (52%)	104 (35%)	37 (13%)	
50-60	204 (46%)	189 (43%)	49 (11%)	
>60	55 (39%)	60 (43%)	26 (18%)	
Race/Ethnicity				.849
Hispanic	54 (50%)	40 (37%)	12 (11%)	
Black	44 (39%)	45 (40%)	21 (19%)	
Asian	46 (47%)	36 (37%)	12 (12%)	
White	257 (47%)	221 (40%)	63 (11%)	
Other	12 (50%)	8 (33%)	4 (17%)	
Education				**.002**
≤ High School	47 (41%)	43 (38%)	24 (21%)	
College	244 (46%)	229 (42%)	71 (13%)	
Graduate School	121 (56%)	71 (36%)	17 (8%)	
Annual household income				**< .001**
< $40,000	32 (31%)	46 (45%)	24 (24%)	
$40,000–$74,999	83 (44%)	76 (41%)	28 (15%)	
$75,000–$99,999	58 (46%)	53 (42%)	16 (13%)	
$100,000–$149,999	80 (46%)	74 (43%)	19 (11%)	
≥ $150,000	139 (60%)	78 (34%)	16 (7%)	
Health literacy				
Lower	21 (51%)	13 (31%)	7 (17%)	.474
Higher	390 (47%)	336 (40%)	105 (13%)	

Differences in distribution for age, education, income and health literacy, were tested using Pearson's chi-square, with significance for P< .05

Table 3.S3: Predicted marginal effects of information exchange and its interaction with risk perception on the treatment decision

Predicted probability of receiving chemotherapy (n=820 complete cases)						
	Knowledge of the recurrence risk		**No knowledge of the recurrence risk**			
	Mean probability	95% CI	Mean Probability	95% CI	Difference	P*
Overall	.303	[.267, .339]	.410	[.333, .486]	**.107**	**.015**
By Perceived Risk						
Very low	.185	[.124, .246]	.367	[.213, .521]	.182	.152
Low	.254	[.199, .309]	.500	[.332, .667]	**.246**	**.024**
Moderate	.382	[.309, 454]	.347	[.221, .472]	-.035	1.00
High/Very high	.521	[.392, .650]	.397	[.181, .612]	-.124	1.00

Mean predicted probabilities with 95% confidence intervals (95% CI), and differences by row (between the two probabilities obtained by level of perceived risk) with P-values (significant if P < .05). n= 820 cases in 168 clusters.

Variance estimation of the mean probabilities and differences was performed using Taylor series approximation applied to the multivariate logistic regression. Odds ratios for the corresponding model are presented in Table 3.5 (Model 2).

* P value adjusted for multiple comparisons using the Bonferroni method.

CHAPTER 4

RACIAL VARIATIONS IN TREATMENT DECISION FOLLOWING GENOMIC TESTING FOR RECURRENCE RISK

4.1 ABSTRACT

Purpose

Genomic tests predicting tumor recurrence for early-stage breast cancer may help inform treatment decisions by identifying patients at low recurrence risk who may forego chemotherapy. Differential use of the test result by race/ethnicity or socioeconomic factors may increase healthcare disparities, and information is needed on the influence of patient preferences and characteristics in this decision process.

Patients and methods

We used a retrospective study design and multivariate analysis to look for patterns of care in a national sample of privately insured women aged less than 65 receiving genomic testing for early-stage breast cancer in 2009–2012. Responses to a mailed survey with oversampling of non-White patients were linked to claims data, and individual recurrence scores (RS) were obtained from the laboratory results. We examined the association of patient self-reported race/ethnicity with variations in RS, and with variations in use of chemotherapy among patients at low and intermediate risks. Multilevel logistic regression models were adjusted for patient age, race/ethnicity, education, income, and other factors that may influence the treatment decision.

Results

Among the 896 respondents, no difference in RS distribution was observed by race/ethnicity. Higher values of RS were significantly associated with higher use of chemotherapy, and the concordance of chemotherapy use with the guidelines was very high (92%). Among patients at low and intermediate risks, higher RS score and being African American were significantly

associated with higher odds of chemotherapy use, and reporting higher opportunity cost of time was significantly associated with lower odds of receiving the treatment, after controlling for other factors.

Conclusion

In a sample of insured women, for whom guideline concordance was high with respect to chemotherapy use, variations in the use of chemotherapy were guided by the result of the genomic test predicting disease recurrence. Among patients at low and intermediate risk, variations in chemotherapy use were observed by race and ethnicity. Determining if variations are associated with differences in clinical factors, patient preferences, patient-physician communication, or provider characteristics, will help guide the design of interventions to improve quality of care.

4.2 INTRODUCTION

While breast cancer remains the second cause of cancer-related deaths for women in the U.S., mortality has steadily declined over the past twenty-five years. Large prospective studies have demonstrated the effectiveness of hormonal therapy and chemotherapy for the treatment of hormonal receptor–positive, lymph node–negative (ER+ LN-) breast cancer; they have also provided evidence that the benefits of adding chemotherapy may not exceed the toll of its toxicity for patients at lower risk of recurrence (Fisher et al., 1989; Fisher et al., 1997; Fisher et al., 2004). Assessing the recurrence risk using a genomic test may help guide treatment decision for ER+ LN- breast cancer, and was added to professional guidelines in 2007-2008 (Harris et al., 2007; NCCN, 2008), a significant change from the previous guidelines that recommended chemotherapy for all patients. Several studies have shown that the use of the genomic test is associated to an overall decrease in the use of adjuvant chemotherapy (Haas et al., 2011a; Hassett et al., 2012; Lyman and Kuderer, 2006; Partin and Mamounas, 2011), and genomic testing was found to change the initial treatment decision for 25-44% of the patients tested (Ademuyiwa et al., 2011; Asad et al., 2008; Henry et al., 2009; Holt et al., 2013; Lo et al., 2010; Rayhanabad et al., 2008).

Little is known on the use of the genomic test in diverse patients populations, and on the communication they receive about it. Indeed, most studies so far have predominantly included non-Hispanic Whites (due in part to higher incidence of ER+ LN– breast cancer in that group) (Lo et al., 2010; Tzeng et al., 2010). This is an important gap in knowledge as studies examining disparities in breast cancer care have identified decision-making and satisfaction about communication of test results as factors influencing treatment and disease outcomes for minority patients (Mojica et al., 2007b; Polacek et al., 2007).

To fill this gap in knowledge we used data from the ECHO study, or *Empowering CHOices for Breast Cancer Treatment*, a national survey of non-elderly, privately insured women, with a large representation of minority women (35%). The dataset includes patient reports on their experience of breast cancer care, and detailed demographic information, complemented by linkage to insurance claims and laboratory results. The present study examines the association of chemotherapy use and race/ethnicity in the context of the test result. In the previous chapters we have explored pathways intervening in the treatment decision, and found significant variations in risk perception and information exchange with race and ethnicity (Chapter 2 and Chapter 3, respectively). We have also documented a significant interaction of risk perception and information exchange on the treatment decision (Chapter 3). In our model, lacking knowledge about the test result was associated with higher odds of chemotherapy use, but this effect was suppressed by the interaction of risk perception and information exchange. Based on the model, we hypothesized that after controlling for age, recurrence score produced by the genomic test (RS), and other factors, the probability of chemotherapy use would be on average higher for African American women compared to White women, as African American women were less likely to know about the test result than White women. In contrast, the counteracting effects of risk perception and knowledge would lessen variations in chemotherapy use for Hispanic women who were more likely to perceive higher risk of recurrence.

4.3 METHODS

4.3.1 Data Source and Population

Data source, population and data collection are described in Chapter 1, Section 1.4.

Briefly, this retrospective study combines data from a patient survey linked to claims information and laboratory records. Eligible participants were women younger than 65 years, who had received a claim for the genomic test Onco*type* DX between January 2009 and November 2012. Based on 2009 claims, 20% of the eligible women were expected to be of minority groups, so those groups were oversampled using information from the health plan or using the Bayesian Improved Surname Geocoding (BISG) method that combines last name and geocoding analysis (Elliott et al., 2008), as described in Chapter 1.

Non-response bias was tested by comparing aggregated information obtained from the health plan on the groups of respondents and non-respondents, including age distribution, year of testing, U.S. Census region, health plan type, and minority status used in the sampling (Table A1).

4.3.4 Measures

Outcome measures

The use of adjuvant chemotherapy during treatment was determined by the existence of claims for the drugs most frequently used for breast cancer care, based on a list established by an expert medical oncologist. Concordance of chemotherapy use with the guidelines was determined based on the use of chemotherapy reported in claims and on the recurrence score (RS). An indicator for guideline concordance was assigned the value 1 if a low-risk patient (RS < 18) did not receive chemotherapy, or if a high-risk patient (RS >30) did receive chemotherapy; and 0, otherwise. This indicator was not applied to the patients at intermediate risk (RS= 18–30) in the absence of clear guidelines for that group.

Patient characteristics

Race/ethnicity was self-reported using the 1997 Office of Management and Budget (OMB) standards, and reclassified into five mutually exclusive categories: Hispanic, Black, Asian, White, and Other (regrouping Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial with no preferred identification with one race). Age at the time of the test was based on claims data. Information on general health status, education, and income was collected in the survey. Demographic indicators based on the survey data included having an annual household income lower or equal to $40,000; having an education level of high school graduate or lower; having a graduate school education; having lower level of health literacy; being employed full-time; being married or in a long-term partnership; having children younger than 18; and having children 18 or older.

The recurrence score (RS) was used both as a continuous variable ranging from 0 to 100, and as a three-level risk indicator. Information on comorbid conditions collected from the health plan were summarized using the Charlson comorbidity index score (Charlson et al., 1987), stratified into 0–1, and 2 or greater. Health plan types (categorized as Point-Of-Service, PPO/Indemnity, and HMO), and dollar amounts paid for the test out-of-pocket by the participants were also collected from the health plan.

Factors that may affect patient-physician communication were measured in the survey, including a score for reporting a good quality of communication, a score for physician mistrust (both described in Chapter 1), and an indicator for patient preference to communicate in a language other than English with their doctor.

Finally, factors that may influence the decision of accepting or not chemotherapy included residing in a rural area (vs. urban/suburban), as it may impact the access to specialty care;

perceived level of family support, opportunity cost of time, and worry about work (all three expressed as summary scores extracted from the survey reports, and described in Chapter 1).

4.3.5 Statistical Analysis

Variable statistics are expressed as mean and standard deviation for continuous variables, and frequency for categorical variables, overall or after stratification by relevant covariates. Summary scores were calculated using principal component analysis with optimization using the Varimax rotation method. Consistency of the scores with the items they represent was verified by correlation analysis. Correlation between variables was tested by the significance of the pairwise correlation coefficients. Bivariate analyses were performed by testing for differences between groups using two-sided Student t-test and one-way analysis of variance (ANOVA) for continuous variables, or Pearson chi-square test for categorical variables.

The probability of receiving chemotherapy among patients at low and intermediate risk was modeled using multilevel logistic regression with adjustment for the clustering of patients by area of residence (CBSA within state). To examine the effect of the recurrence score close to the boundary between low and intermediate risk (*i.e.*, between RS 17 and 18), the value of the recurrence score used in the regression models was recentered at the value 17.5. The effect of clustering on the variance of the error term was evaluated using the intraclass correlation (ICC). Series of multilevel logistic regression analyses were performed to assess the effect of race/ethnicity on the outcome with the progressive addition of covariates corresponding to domains in our conceptual framework. Each individual model can be summarized as:

$$Y_{\text{Chemotherapy use}} = \beta_0 + \beta_1 * \text{Hispanic} + \beta_2 * \text{Black} + \beta_3 * \text{Asian} + \beta_4 * \text{Other} + \Sigma (\alpha_i * \text{covariate}) + RE + \varepsilon$$

where $Y_{\text{Chemotherapy use}}$ is the log odds of the probability of chemotherapy use, $\beta 0$ is the fixed intercept, β_1 to β_4 are the fixed-coefficients for the racial/ethnic categories (White is the reference group), RE represents the random-effects components accounting specific for CBSA and states, ε represents the residual error term, and the fixed effects for the covariates Σ (α_i *covariate) are:

Σ [Model 1] = α_1 * RS + α_2 * age + Σ (α_j * health) + Σ (α_j * year)

Σ [Model 2] = Σ [Model 1] + Σ (α_j * education) + $\alpha 4$ * lower income

Σ [Model 3] = Σ [Model 2] + Σ (α_j * health plan type)

Σ [Model 4] = Σ [Model 3] + α_5 * communication + α_6* mistrust

+ α_7 * language + α_8 * health literacy

Σ [Model 5] = Σ [Model 4] + +α_9 * family support + α_{10}* opportunity cost

+ α_{11} * worry about work + α_{12} * rural residence + Σ (α_j * kids)

All models included an indicator variable for the year of testing to account for the effect of time. All models were run on the sample corresponding to the full model, and differences in fit between models were evaluated using a log likelihood ratio test. The predictive power of the logistic models was evaluated as the area-under-the-curve

No covariate in the models had more than 10% of missing values, so the analysis was performed on complete cases. To test for potential selection bias, the characteristics of the complete cases were compared with those of the cases with missing values (Table 4.S1). Among patients at low–intermediate risk, patients with missing values were slightly older (average age, 54 years vs. 52 years for complete cases), more often reported a lower health status, lower SES, and lower health literacy (all, $P < .05$); there was no significant differences for the other covariates present in the model, including recurrence score, chemotherapy use, race/ethnicity, year of treatment, and region (Table 4.S1).

Variances of predictive margins effects were estimated using Taylor Series approximation applied to the fixed components of the multilevel models. As a sensitivity analysis, the multilevel logistic regression (Full model) was compared to equivalent models using simple logistic regression, or random-effects logistic regressions, adjusted for clustering of patient residence (cluster unit = CBSA); those models resulted in similar coefficients estimates. Finally, we compared the effect of adjusting the multilevel logistic model for clustering by site of medical care (city within state for the provider ordering the test), instead of using patient area of residence (CBSA within state); the two approaches resulted in the same results.

Throughout the study, estimates were considered significant for P-value lower than 0.05, and marginally significant for P-value lower than 0.1. All analyses were performed on STATA 13 (Stata Corp., College Station, TX).

4.3 RESULTS

4.3.1 Patient characteristics

Demographic characteristics of the respondents were analyzed after stratification by self-reported race/ethnicity, with the sample including 108 Hispanics, 112 Blacks, 97 Asians, and 549 non-Hispanic Whites (Table 4.1). Overall, the mean age of the patients was 52 years (SD 7; range 29-64), with 34% aged less than 50. Asian patients were on average younger, with 48.5% aged less than 50. While the education level of the cohort was high overall, the frequency of low education level (high school graduate or lower) was significantly higher among Hispanics. Reports of low household income were significantly more frequent among Hispanic and Black women. Black women were reporting more often to work full time, and less often to be married or in a long-term relationship (Table 4.1).

Significant differences in health plan types were found between racial/ethnic groups, but were likely linked to regional differences in health plan offering and uptake, as the correlation between health plan types and U.S. Census regions was stronger than the correlation between health plan types and race/ethnicity (absolute value of the pairwise correlation coefficients: rho=0.12, $P < .05$, and rho=0.03, $P= .374$, respectively). Information from claims on dollar amounts paid by patients for the test was available for 783 participants, with 63.4% receiving full coverage. The average amount for those who paid out-of-pocket was $492 (median $360; n=213), and 16 patients paid more than $1000. Members with a copay tended to be enrolled in PPO/Indemnity plans; we found no significant difference in out-of-pocket amounts by race/ethnicity.

Quality of the communication with the physician was examined using different domains probed in the survey (Table 4.S2). Compared to the other groups, Hispanic women more frequently reported a lower confidence in filling medical forms, which may have related to a higher preference for using a language other than English with their doctors (pairwise correlation coefficient between language and confidence: 0.37, $P < .05$ for the Hispanic group; $P> .05$ for the other groups). Regarding patient-physician interaction, we found no significant differences in reports of good communication with the physician, but Asian women expressed significantly higher level of physician mistrust than the other groups ($P= .007$). Among other factors that may influence treatment decisions, family support was significantly stronger for White and Hispanic patients, and lower for Black women; Hispanic and Asian reported greater influence of opportunity cost of time; and Black women expressed significantly higher levels of worry about work (all $P \leq .001$; Table 4.S2).

Most women reported generally excellent or very good health (64%). The mean value for the Charlson Index score was 1.85 SD (SD 0.99), and scores greater or equal to 2 were more frequent observed among Black and White non-Hispanic women (65.2 and 66.5%) than among Hispanic and Asian women (56.5% and 49.5%; P= .037). Looking at the medical procedures received for breast cancer treatment, a majority of the women were treated with breast-conserving surgery followed by radiation therapy (62%), and 32% received a mastectomy. No significant differences in the rates of surgery types and radiation therapy were found by race/ethnicity. The genomic test confirmed the ER+ status and Her2– status for more than 97% of the patients.

4.3.2 Recurrence risk based on the genomic test and chemotherapy treatment

Among the respondents, 55% of the patients were identified at low recurrence risk, 35% at intermediate risk and 10% at high risk (Table 4.2). No difference in the distribution of the recurrence score (RS) was observed by race/ethnicity (Figure 4.1A and Table 4.2). Use of chemotherapy varied by risk, as expected, with low rates among the low-risk patients (8 %) and higher rates among the high-risk patients (89%), resulting in a very high concordance with the treatment guidelines (92%; Table 4.2). After stratification by race/ethnicity, the use of chemotherapy was marginally higher for Hispanic and Black patients at low recurrence risk (P = .077), and the concordance of care with the guidelines was very high for all racial/ethnic groups (all >85%, P= .067; Table 4.2).

Patient characteristics significantly associated with chemotherapy use included younger age (P= .016), and lower score for opportunity cost of time (P < .001; Table 4.3). Among intermediate-risk patients, patients receiving chemotherapy more often had a lower Charlson score of 0-1 (P= .02), were more often parents of children aged less than 18 (P= .043), and

tended to score lower on the metric for good communication with the physician (P= .074). In contrast, among low-risk patients, chemotherapy receipt was significantly lower for patients with lower income, and for women with adult children; the difference in age between chemotherapy users and non-users was larger among low-risk patients compared to the two other risk groups. Patients at low risk who received chemotherapy, were significantly younger compared to those who did not (mean age, 49 years vs. 53 years, P < .001; Table 4.3).

After stratification by treatment group among low-risk patients, chemotherapy receipt was associated with higher recurrence scores for Hispanic and Black patients compared to White patients (Figure 4.1B, Table 4.4). In contrast, among intermediate-risk patients, higher values of the recurrence score were associated with chemotherapy receipt for Asian patients, whereas the difference in risk scores was not significant for Black patients (Table 4.4). Those observations suggested that race/ethnicity might be associated with variations in treatment decision. We examined this association further using multilevel logistic regression analysis to control for confounding factors such as age, education and income.

4.3.3 Variations in the probability of chemotherapy use among patients at low and intermediate risks

We modeled the probability of receiving chemotherapy among low and intermediate-risk patients using a series of multilevel logistic regression guided by our conceptual framework (Table 4.5). The first model included the RS as a continuous score recentered at the cutoff value 17.5, and also race/ethnicity, age, health status, and year of testing (Table 4.5, Model 1). The model was sequentially completed by adding blocks of covariates corresponding to SES (Model

2), health plan types as a proxy for medical system elements (Model 3, "+ system"), patient-physician interaction (Model 4 "+ communication") and factors susceptible to influence the decision of chemotherapy (Model 5, "Full model"). As expected the recurrence score was the strongest predictor for receiving chemotherapy in all models (Table 4.5). Younger age was also a determinant for chemotherapy use. Being African American was significantly associated with increased odds of receiving chemotherapy after controlling for SES and system elements. Patient's higher mistrust of the physician was significantly associated with lower odds of chemotherapy use in Model 4. Reporting a higher opportunity cost of time was associated with lower odds of receiving chemotherapy in the full model (Table 4.5, Model 5).

After controlling for all other factors (Model 5), among low and intermediate risk patients, the probability of Black patients to receive chemotherapy was on average 12.6 percentage points higher than for White women with similar characteristics, after controlling for random effects in the model (P= .022; Table 4.S3).

4.3.4 Variations in the probability of chemotherapy use by race/ethnicity at the cutoff between low and intermediate risks

Uncertainty about what may be the best treatment option may be higher for patients with RS close to the boundary between low and intermediate risks. A one-point increase in RS at scores 17–18 results in a change in treatment recommendations; however, the absolute difference in recurrence rate at 10 years between the those two patients is actually small (about one-percentage point; Paik et al., 2004). So it is likely that for some patients the actual recurrence score may be more influential in the treatment decision than the risk category. Based on the differences in RS distribution observed after stratification by race/ethnicity and treatment (Figure 4.1B), we

hypothesized that patterns of treatment close to the boundary between low and intermediate risks may vary with race/ethnicity.

Using the fully adjusted model (Table 4.5, Model 5) we plotted the predicted probabilities of receiving chemotherapy over the recurrence score, and looked at the differences in fitted probabilities after stratification by race and recurrence risk. There was a significant shift in the probability of receiving chemotherapy at the boundary between low and intermediate risks, and the increase was bigger for Black patients than for White patients (Figure 4.2). The average risk difference was 17 percentage points between Black and White patients at RS =17 (P= .066), and 20 percentage points at RS =18 (P= .044, both using Bonferroni adjustment for multiple comparisons).

To contextualize the effect of race/ethnicity, we compared the effect of being Black vs. White with the effect of age that is a factor known to be influential in treatment decisions. We plotted the predicted probability of receiving chemotherapy over the recurrence score after stratification by age 50 or more, vs. age less than 50 (Figure 4.S1). The similarity between the plots obtained after stratification by race or by age suggests that the effect of race was comparable in magnitude to the effect of age. A similar pattern was obtained by stratifying the patients based on the distribution of the score measuring opportunity cost of time that was also a significant barrier to receiving chemotherapy in the model. In this case, patients scoring at the 75th percentile or higher for opportunity cost had a lower probability of use than those scoring below the 75th percentile, and the difference in probability of chemotherapy use by opportunity cost of time was significant among patients at intermediate risk (Figure 4.S1).

4.4 DISCUSSION

Among low and intermediate risks patients, the recurrence score produced by the test was the strongest determinant of chemotherapy use in our model using multilevel logistic regression. Other factors associated with increased odds of chemotherapy use included younger age, lower opportunity cost of time and being African American. On a plot for the predicted probability of chemotherapy use, significant differences between Black and White patients were observed among intermediate-risk patients. While the probability of receiving chemotherapy was significantly higher in the intermediate-risk category compared to the low-risk category for both races, the shift was more marked for Black patients than for White patients.

While we find variations in treatment decision by race among intermediate-risk patients, we also found a very high concordance of the use of chemotherapy with the guidelines. Over 90% of the patients to whom ASCO and NCCN guidelines applied (Harris et al., 2007; NCCN, 2008) had received appropriate care. This high adherence rate compares to existing benchmarks from a comprehensive report on the quality of care for patients with breast cancer (Malin et al., 2006). In the present study, only a few high-risk patients did not receive chemotherapy, and the lack of chemotherapy use may relate to the existence of comorbid conditions, or strong patient preferences (among the 10 patients at high risk not receiving chemotherapy, 4 had a Charlson index score of 2 or greater, and 3 reported an aversion for chemotherapy in the survey). Among low-risk patients the use of chemotherapy was very low for all racial/ethnic groups, but higher proportions of Black and Hispanic patients had received chemotherapy compared to White and Asian women. Differences in treatment were not explained by age differences solely. Among low-risk patients, White women who received chemotherapy were on average younger than White women who did not (mean age, 48 years (SD 8) vs. 53 years (SD 6), respectively, P

<.001), but the difference in age by treatment group was not significant for Hispanic and Black women at low risk (mean age 52 years (SD 8, n=8, n=22) vs. 50 years (SD 8, n=46, n=293), P =.593, and mean age 51 years (SD 8, n=6) vs. 54 years (SD 6, n=50), respectively, P =.249). The slightly higher rates of chemotherapy may be explained by differences in clinical features omitted in the dataset.

Variations in chemotherapy use may also relate to differences in practice. As the incidence of aggressive breast cancer is higher for Black women, it is possible that physicians treating predominantly Black patients may adopt a more conservative treatment approach as recommended by previous guidelines and offer chemotherapy even in the case of ER+ LN- breast cancers with low recurrence score. Previous studies sufficiently powered to look at the effect of race/ethnicity did not detect differences in treatment between Black and White women after receiving the genomic test in the years 2005-2009 (Guth et al., 2013; Lund et al., 2012). However, both studies were limited to specific geographic areas (New York City, NY, and Atlanta, GA, respectively), so it is difficult to evaluate the external validity of those findings.

Patient preferences may also result in more conservative care, as documented for decisions about the type of surgery for breast cancer (Collins et al., 2009; Hawley et al., 2009; Katz and Hawley, 2007). Differences in patient knowledge about surgery outcomes have been shown to affect the decision between breast-conserving surgery and mastectomy, with less informed women choosing mastectomy. Patient preferences were sensitive to information using decision aids that provided information on the similarity of surgery outcomes (Waljee et al., 2007) Those results support that the communication about the test result and its clinical implications may facilitate the treatment decision. Furthermore, patients who perceive in the long term that they

had more control in the decision are more likely to be satisfied with their decision (Street and Voigt, 1997). Therefore, educating patients about what to expect before the visit may help them feel more empowered to participate in decision-making

In the model controlling for communication factors (Table 4.5, Model 3), physician mistrust was significantly associated with lower odds of chemotherapy. Lower quality of patient-physician that may arise from mistrust is likely to result in lower satisfaction of the patients about the care received, and may impact long-term outcomes (Bickell et al., 2012). Cultural discordance and language barriers may further complicate the task if providers feel insufficiently trained in how to communicate about new technologies with diverse populations of patients (Allford et al., 2013). Supporting physicians in better communicating about personalized medicine may also improve communication for patients at lower levels in education and health literacy, as those patients are more likely to have difficulties in interpreting risk and understanding probabilities (Davis et al., 2002).

Opportunity cost of time was also significant in the model. It may relate directly to economic factors, such as ability to work, or transportation needs, but also to the family situation including needs for childcare; in contrast, the support from adult children helping during the treatment period may be determinant in accepting a treatment that a patient may have refused otherwise. Helping physicians identify factors that are barriers or facilitators ahead of the treatment decision may help in engaging the discussion, and in supporting the patient's assessment of what her best personal option may be in case of medical uncertainty. Further research is needed at this point to identify actionable targets for intervention, but one can already envision that those interventions would aim 1) to promote patient engagement and education to be better prepared to make an informed treatment decision; and 2) to support physicians to

communicate effectively about the test significance and increase the chance of a shared decision taking in account clinical factors as well as patients preferences.

This study has a number of strengths that allowed addressing the effects of race/ethnicity on the treatment decision. First, the sampling strategy and high response rate resulted in a diverse sample with enough analytic power to look at individual racial/ethnic groups, and to detect effects that would have been masked by aggregating all non-White patients together. Also the overall high SES level observed across all racial/ethnic groups sample may help disentangle the effect of race/ethnicity, income and education, compared to other studies where the difference in SES were more marked between White and non-White patients.

Another strength of this study is the combination of objective data from claims and laboratory records with survey information. The use of claims data with the eligibility criteria (first episode of early-stage ER+ LN–breast cancer, and enrollment in a national commercial insurance plan) resulted in a sample likely to be more homogenous in term of clinical characteristics and access to care than using data from a cancer registry. Also, aggregated claims data provided information on the non-respondent group to test for selection bias using patient demographic statistics. However, selection may have also resulted from differences in treatment if the patients receiving chemotherapy more recently tended to participate at lower rates in the survey. While we have no information on the treatment received by the non-respondents, we found no significant variation in chemotherapy receipt by year of treatment, whereas there was a trend for higher proportion of respondents diagnosed at high-risk in 2009 compared to more recent years (18% among all respondents treated in 2009 respondents vs. < 10% in 2010–2012,

P=.075). Therefore, it is likely that participation rates may have been affected more by the severity of the diagnosis, than by the type of treatment.

Limitations of the study include the retrospective study design with a recall time of up to four years. To address this, all models were adjusted for time. It is worth noting that recall bias should not affect the outcome measures collected from claims and laboratory records, but as the test has become more common with time it is possible that the dissemination of the guidelines would have also increased over the period of time, or that treatment pattern may have changed as physician gained familiarity with using the test in practice. We found no evidence in the analysis for a significant change in the period 2009 to 2012.

We are lacking information on tumor characteristics and other factors such as family history that may have influence the final treatment decision in addition to the result of the genomic test. The preauthorization controlled for part of those characteristics, but we have no indication on the distribution of tumor stage I and stage II by race and ethnicity. Higher frequency of more advanced stages among Black and Hispanic patients may explain the higher frequency of chemotherapy use compared to White patients.

Also, we have no information on the potential enrollment of respondents in clinical trials, enrollment that may have affected treatment decisions. Recruitment for the TAILORx trial evaluating the benefit of chemotherapy for the intermediate group was ongoing from April 2006 to October 2010 and from July 2011 to December 2012 (NIH, 2006). We cannot exclude that some of the survey participants were enrolled in TAILORx, or that the ongoing trial may have influenced patterns of care outside of the TAILORx study. The patient classification in TAILORx uses a different framework, with chemotherapy avoidance stopping at RS = 11, and

all patients at RS > 25 receiving chemotherapy (Sparano, 2006). However, we found no evidence for differences in chemotherapy use by year of treatment, and around the RS 11 and 25 used as cutoffs in TAILORx.

The study was limited to a privately insured population who had access to the test and may not be typical of the whole patient population who may benefit from receiving a genomic test during their breast cancer care. It is difficult to determine if our findings would apply to an older population, or to patients who are not covered for the cost of this expensive test (about $4,000). However, the test is now widely covered, including by Medicaid in 35 states (Genomic Health, 2004), so it is not limited to non-elderly patients with commercial plans or higher levels of income. The survey was administered in English only. Finally, information on the providers is at this point limited to geographic information, and it does not allow assessing provider-related factors that may influence the use of the genomic test in treatment decision. Finally, the logistic regression analyses were performed on complete cases only, and the cases with missing values tended to have lower SES and to be older. As both greater age and lower SES were associated with lower odds of chemotherapy use, it is likely that a selection bias would result in estimates biased toward zero.

New and costly technologies may be unaffordable for uninsured and low-income populations. Technology diffusion may be slower in medical centers delivering care to populations with lower resources, further increasing disparities (Coughlin et al., 2008; Link et al., 1998). Beyond access and costs, personalized medicine might worsen health disparities by increasing the role of patient-physician interaction and patients' involvement in decision-making. Lower levels in education and health literacy may penalize patients when it comes to interpreting risk and understanding probabilities inherent to personalized medicine (Davis et al., 2002).

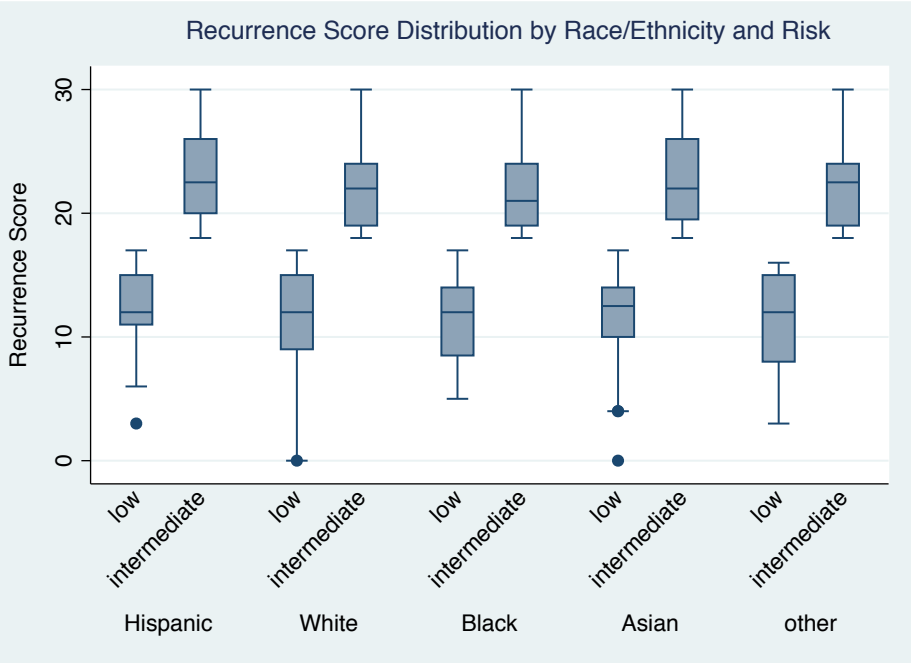
Cultural discordance and language barriers may further complicate the task if providers feel insufficiently trained in how to communicate about those new technologies (Allford et al., 2013).

Interventions may target providers to increase their familiarity with the test and improve communication around the test result; in particular, providing scripts or vignettes may help physicians in starting the discussion with their patients. Interventions should also include patient components including the use of screening questions to probe patient preferences and information needs before initiating the chemotherapy discussion; informing patients about the existence of the test before the visit might increase patient engagement and help patients prompt the discussion if the physician does not initiate it.

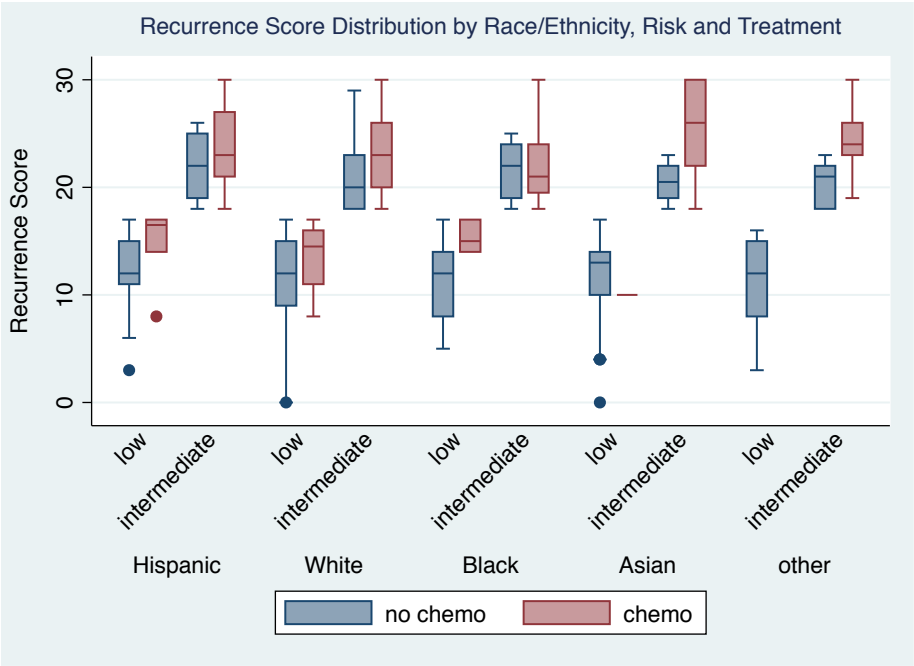
4.5 FIGURES AND TABLES

Figure 4.1: Distribution of the recurrence scores by race/ethnicity among low and intermediate-risk groups (A), and after stratification by race/ethnicity and chemotherapy use (B)

A.

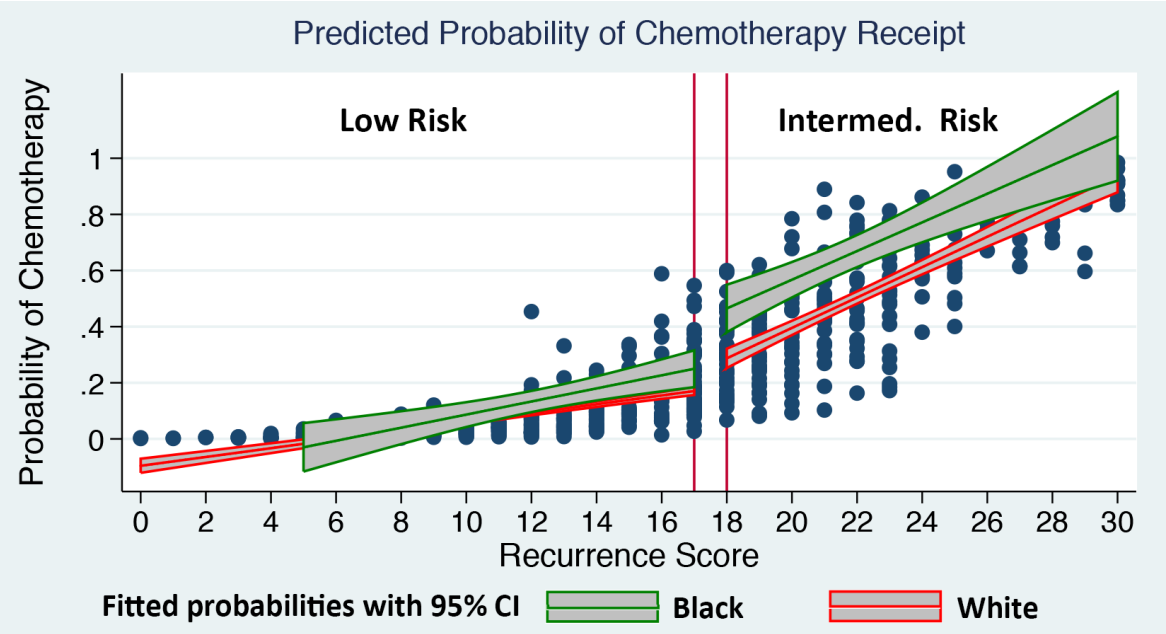


B.



Recurrence score distributions are summarized using box-and-whisker plots in which the box covers the 25th to 75th percentiles, and the line within the box indicates the median; whisker ends show the most extreme values, or values within 1.5 interquartile of the quartile; outliers are indicated by dots. Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Figure 4.2: Variations in the predicted probability of chemotherapy use between Black and White patients at low and intermediate risk



The predicted probability of receiving chemotherapy among low and intermediate-risk patients was predicted using the full model for multilevel logistic regression presented in Table 4.5.
The plot features the predicted probabilities (based fixed components and random components) for individual patients at low and intermediate risks (grey dots), and the fitted values and 95% confidence intervals for groups of interest after risk stratification (low vs. intermediate): Black patients (green, n=64), and White patients (red, n=414). Non-overlapping 95% confidence intervals (in grey) indicate significant differences between groups. The vertical bars (red) mark the cutoffs between as low risk (<18) and intermediate risk (18–30).

Table 4.1: Characteristics of the survey respondents, overall and by race/ethnicity

Characteristics	All Women n = 896†	Hispanic n = 108 (12.1%)	Black n = 112 (12.6%)	Asian n = 97 (10.9%)	White n = 549 (61.7%)	Other[1] n = 24 (2.7%)	*P*
Age at test	52.0 (7.0)	51.2 (7.3)	52.3 (6.9)	49.9 (7.0)	52.5 (6.8)	50.8 (7.6)	**.007**
Age range (years)	[29–64]	[33–64]	[30–63]	[33–64]	[29–64]	[30–62]	
< 50 years	301 (34%)	44 (41%)	37 (33%)	47 (49%)	164 (30%)	9 (38%)	**.016**
Education							**<.001**
≤ High school	115 (13%)	23 (21%)	13 (12%)	2 (2%)	75 (14%)	2 (8%)	
College	556 (62%)	67 (62%)	72 (64%)	67 (69%)	339 (62%)	11 (46%)	
Graduate school	218 (24%)	18 (17%)	27 (24%)	27 (28%)	135 (25%)	11 (46%)	
Household Income, annual							**<.001**
< $40,000	105 (12%)	22 (20%)	25 (22%)	7 (7%)	49 (9%)	2 (8%)	
$40,000–$74,999	190 (21%)	38 (35%)	36 (32%)	15 (16%)	98 (18%)	3 (13%)	
$75,000–$99,999	130 (15%)	15 (14%)	13 (12%)	14 (14%)	83 (15%)	5 (21%)	
$100,000-$149,999	175 (20%)	8 (7%)	12 (11%)	5 (5%)	67 (12%)	3 (13%)	
≥ $150,000	235 (26%)	15 (14%)	14 (13%)	37 (38%)	163 (30%)	6 (25%)	
Full-time employed	521 (58%)	65 (60%)	83 (74%)	63 (65%)	295 (54%)	12 (50%)	**.006**
Married/long term partner	651 (73%)	80 (74%)	52 (46%)	78 (80%)	415 (76%)	20 (83%)	**<.001**
Children < 18 years	220 (25%)	31 (29%)	14 (13%)	33 (34%)	137 (26%)	5 (21%)	.054
Children ≥ 18 years	543 (61%)	67 (62%)	79 (71%)	51 (53%)	328 (60%)	13 (54%)	.327
Health plan type							**<.001**
Point of Service	702 (78%)	77 (71%)	68 (61%)	76 (78%)	456 (83%)	19 (79%)	
PPO/Indemnity	90 (10%)	12 (11%)	7 (6%)	16 (17%)	52 (10%)	3 (13%)	
HMO	102 (11%)	40 (7%)	37 (33%)	5 (5%)	40 (7%)	2 (8%)	
Year of treatment							.866
2009	115 (13%)	13 (12%)	13 (12%)	16 (16%)	70 (13%)	3 (135)	
2010	197 (22%)	22 (21%)	23 (21%)	20 (21%)	125 (23%)	4 (17%)	
2011	267 (30%)	39 (36%)	30 (27%)	26 (27%)	164 (30%)	6 (25%)	
2012	315 (35%)	33 (31%)	46 (41%)	35 (36%)	189 (34%)	11 (46%)	
U.S. Census region							**<.001**
Northeast	205 (23%)	20 (19%)	28 (25%)	26 (27%)	125 (23%)	2 (8%)	
North Central	100 (11%)	4 (4%)	8 (7%)	5 (5%)	80 (15%)	1 (4%)	
South	430 (48%)	65 (60%)	73 (65%)	35 (36%)	244 (44%)	13 (54%)	
West	159 (18%)	18 (17%)	3 (3%)	31 (32%)	99 (18%)	8 (33%)	

Continuous variables, mean (SD); categorical variables, frequencies (percent given by columns). Differences in means tested between groups using ANOVA and differences in distribution tested using Pearson's chi-square. Missing values < 5%, except for income reports (missing 7%). Race/ethnicity is based on self-report and recoded as 5 mutually exclusive categories; † race/ethnicity is unknown for 6 respondents; claims and laboratory data are missing for 2 respondents (0.2%). [1] Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Table 4.2: Recurrence risk, chemotherapy receipt and guideline concordance, overall and by race/ethnicity

Characteristics	Overall n = 896†	Hispanic n = 108 (12.1%)	Black n = 112 (12.6%)	Asian n = 97 (10.9%)	White n = 549 (61.7%)	Other[1] n = 24 (2.7%)	*P*
Recurrence risk							.289
Low (RS <18)	492 (55%)	54 (50%)	56 (50%)	54 (56%)	315 (57%)	11 (46%)	
Intermediate	310 (35%)	42 (39%)	35 (31%)	36 (37%)	184 (34%)	10 (42%)	
High (RS> 30)	92 (10%)	11 (10%)	21 (19%)	7 (7%)	49 (9%)	3 (13%)	
Chemotherapy received							
Overall	279 (31%)	42 (39%)	43 (38%)	26 (27%)	160 (29%)	8 (33%)	.098
% Risk Category							
Low	37 (8%)	8 (15%)	6 (11%)	1 (2%)	22 (7%)	0 (0%)	**.077**
Intermediate	161 (52%)	23 (55%)	20 (57%)	18 (50%)	95 (52%)	5 (50%)	.967
High	82 (89%)	11 (100%)	17 (81%)	7 (100%)	43 (88%)	3 (100%)	.397
Guideline concordance*							
(n= 581)	534 (92%)	57 (88%)	67 (87%)	60 (98%)	336 (92%)	14 (100%)	**.067**

P < .1 are marginally significant, P < .05 are significant.
Continuous variables, mean (SD); categorical variables, frequencies (percent given by columns). Differences in means tested between groups using ANOVA and differences in distribution tested using Pearson's chi-square. Unless specified, the number (percent) of missing values for individual variables is less than 5%, overall. ‡ 10 of the high-risk patients did not receive chemotherapy because of strong patient preferences against this treatment option or of comorbid conditions based on survey reports and claims data.

* Guideline concordance applied to high risk and low risk patients only, with value 1 if a high risk patient received chemotherapy or if a low risk patient did not get chemotherapy, based on the guidelines from ASCO and NCCN; risk category is based on laboratory recurrence scores lower than 18 or greater then 30, and receipt of chemotherapy is indicated by the existence of claims for chemotherapy drugs.

Race/ethnicity from self-reports was recoded as 5 mutually exclusive categories; † race/ethnicity is unknown for 6 respondents; claims and laboratory data are missing for 2 respondents (0.2%). [1] Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Table 4.3: Comparisons of patient characteristics after stratification by chemotherapy receipt and by recurrence risk

	Overall		Low Risk		Intermediate Risk		High Risk	
Chemotherapy	Yes	No	Yes	No	Yes	No	Yes	No
	n=282	n=612	n=37	n=455	n=163	n=147	n=82	n=10
Recurrence Score	**28 (12)**	**14 (6)****	**14 (3)**	**12 (4)****	**23 (4)**	**2 (3)****	43 (10)	40 (10)
Age	**51 (7)**	**53 (7)***	**49 (8)**	**53 (7)****	**51 (7)**	**53 (8)***	52 (7)	51 (9)
Charlson Score ≥ 2	41%	34%	49%	35%	44%	31%*	**32%**	**60%**
Income < $40,000	10%	12%	**0%**	**13%****	10%	10%	13%	30%
≤ High school	30%	28%	11%	12%	13%	12%	17%	10%
Graduate school	26%	24%	35%	23%	27%	26%	21%	10%
Adult children	**56%**	**64%***	**46%**	**66%***	55%	58%	64%	60%
Children < 18 years	29%	23%	35%	24%	**31%**	**21%***	22%	20%
Communication	-.06	.03	.09	.02	-.16	.04	.08	.12
	(.99)	(1.00)	(.95)	(1.02)	(1.01)	(.95)	(.97)	(1.09)
Physician mistrust	-.01	.01	-.24	.03	.03	.12	.01	-.01
	(.99)	(1.00)	(.90)	(.96)	(1.03)	(1.10)	(.95)	(1.35)
Family support	.05	-.03	.23	-.05	-.00	.08	.06	-.58
	(1.04)	(.98)	(.90)	(.98)	(1.12)	(.94)	(.93)	(1.47)
Opportunity cost	**-.21**	**.11****	**-.49**	**.07****	**-.09**	**.20***	-.31	.05
	(.96)	**(1.00)**	**(.95)**	**(1.00)**	**(.95)**	**(1.02)**	(.95)	(1.05)
Worry about work	.05	-.02	.21	-.08	.03	.12	.02	.05
	(1.00)	(1.00)	(.92)	(1.00)	(1.01)	(.98)	(1.04)	(.91)

* P < .05 **P<.001

Continuous variables reported as means (SD); categorical variables reported as percentages.

Differences between treatment groups tested using two-sided test of proportions, or two-sided t-tests for differences in means. No differences in distribution were observed by year of testing or Census region, using Pearson's chi-square.

For the high-risk patients, differences were significant at the 10% level for Charlson Score ≥ 2 and for family support score.

Table 4.4: Mean recurrence scores by treatment group after stratification by race/ethnicity and risk category

	Low Risk			Intermediate Risk		
Chemotherapy	Yes	No	Difference	Yes	No	Difference
Hispanic	15	12.3	2.7*	24	21.7	2.3*
Black	15.3	11.2	4.1**	22.0	21.7	0.3
Asian	(10)	12.0	-	25.2	20.3	4.9**
White	13.4	11.5	1.9*	23.1	20.9	2.3**
Overall	14.0	11.6	2.3**	23.4	21.0	2.4**

* P < .05, ** P < .01.

Differences between the mean RS for the women receiving chemotherapy and the mean RS of those who did not were tested using two-sided t-test after stratification by race/ethnicity and risk category. All differences in means were significant at the 5% level, except for Black patients at intermediate risk. Only 1 Asian patient at low risk received chemotherapy so the difference in mean was not tested for Asian women at low risk.

Table 4.5: Odds ratios for the probability of receiving chemotherapy among low and intermediate–risk patients

Odds Ratios	n= 647 Patients at Low and Intermediate Risk									
	Model 1 Base model		Model 2 + SES		Model 3 + System		Model 4 + Communication		Model 5 Full model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
RS score#	**1.32*** **	**[1.26,1.39]**	**1.32*** **	**[1.26,1.39]**	**1.32*** **	**[1.26,1.39]**	**1.33*** **	**[1.26,1.40]**	**1.33*** **	**[1.27,1.40]**
Race/Ethnicity										
White (ref.)	1	-	1	-	1	-	1	-	1	-
Hispanic	0.95	[0.48,1.90]	1.05	[0.52,2.11]	1.09	[0.54,2.17]	1.1	[0.54,2.25]	1.32	[0.65,2.72]
Black	2.05	[1.00,4.22]	2.07	[0.99,4.31]	**2.24***	**[1.05,4.78]**	**2.28***	**[1.06,4.91]**	**2.62***	**[1.18,5.82]**
Asian	0.54	[0.24,1.19]	0.49	[0.22,1.09]	0.48	[0.22,1.07]	0.57	[0.25,1.28]	0.77	[0.33,1.81]
Other	0.54	[0.14,2.07]	0.47	[0.12,1.84]	0.47	[0.12,1.82]	0.49	[0.12,1.96]	0.47	[0.11,1.92]
Age	**0.95****	**[0.92,0.98]**	**0.95****	**[0.92,0.98]**	**0.95****	**[0.92,0.98]**	**0.95****	**[0.92,0.98]**	**0.96***	**[0.92,1.00]**
Health										
Excellent (ref.)	1	-	1	-	1	-	1	-	1	-
Very Good	1.07	[0.58,1.95]	1.17	[0.63,2.18]	1.16	[0.63,2.15]	1.19	[0.64,2.23]	1.19	[0.63,2.25]
Good	1.39	[0.71,2.73]	1.63	[0.81,3.27]	1.64	[0.82,3.29]	1.66	[0.82,3.39]	1.7	[0.83,3.49]
Fair/Poor	1.23	[0.42,3.60]	1.94	[0.63,6.03]	2.02	[0.66,6.23]	2.14	[0.69,6.61]	2.26	[0.69,7.40]
Year of testing										
2009	1.05	[0.49,2.27]	1.06	[0.49,2.27]	1.03	[0.48,2.19]	1.03	[0.48,2.21]	0.99	[0.46,2.14]
2010	1.26	[0.69,2.30]	1.28	[0.70,2.35]	1.26	[0.69,2.31]	1.31	[0.71,2.43]	1.32	[0.71,2.46]
2011	1.25	[0.72,2.18]	1.31	[0.75,2.29]	1.3	[0.74,2.28]	1.29	[0.73,2.29]	1.26	[0.71,2.26]
2012	1	-	1	-	1	-	1	-	1	-
SES										
≤ High school graduate			0.79	[0.38,1.67]	0.8	[0.38,1.69]	0.71	[0.33,1.56]	0.79	[0.35,1.77]
Graduate school			1.14	[0.68,1.90]	1.15	[0.69,1.92]	1.15	[0.69,1.93]	1.01	[0.59,1.72]
Income < $40,000			**0.40***	**[0.16,0.97]**	**0.40***	**[0.16,0.97]**	0.43	[0.17,1.05]	0.42	[0.17,1.07]
Health plan type										
Point-Of-Service (ref.)					1	[1.00,1.00]	1	[1.00,1.00]	1	[1.00,1.00]
PPO/Indemnity					0.86	[0.38,1.95]	0.84	[0.36,1.94]	0.75	[0.31,1.77]
HMO					0.67	[0.33,1.38]	0.71	[0.34,1.47]	0.82	[0.39,1.73]
Interaction with physician										
Communication							0.78	[0.58,1.04]	0.79	[0.60,1.05]
Physician mistrust							**0.73***	**[0.54,0.98]**	0.77	[0.58,1.03]
Language other than English							0.57	[0.11,3.06]	0.65	[0.12,3.60]
Lower health literacy							1.39	[0.43,4.46]	1.49	[0.46,4.80]
Facilitators and barriers										
Family support									0.98	[0.75,1.27]
Opportunity cost of time									**0.68****	**[0.53,0.87]**
Worry about work									0.93	[0.72,1.21]
Rural Residence									1.36	[0.69,2.70]
Adult children									0.88	[0.51,1.52]
Children <18									1.36	[0.73,2.52]
Log likelihood	-256.86		-253.78		-253.16		-250.33		-244.59	
Chi2	123.77		124.7		127.5		126.53		132.42	
AIC	543.71		543.56		544.32		546.65		547.17	

* p<0.05, ** p<0.01, *** p<0.001

N= 647 complete cases in 164 CBSA within 41 states. Odds ratios were estimated using a series of multilevel logistic regression with the progressive addition of covariates mapping to the domains of our conceptual framework. The area under the curve for the full model ROC is 0.897, with 95%CI (0.873, 0.921). The effect of clustering in the model was small with ICC ≤ 2% at each level. The fit of the model was significantly improved by the inclusion of all the covariates in Model 5 compared to the base model (Model 1) as shown by the significance of the log likelihood ratio test for nested models with a P value = .0394 for chi2(14, 24,54).

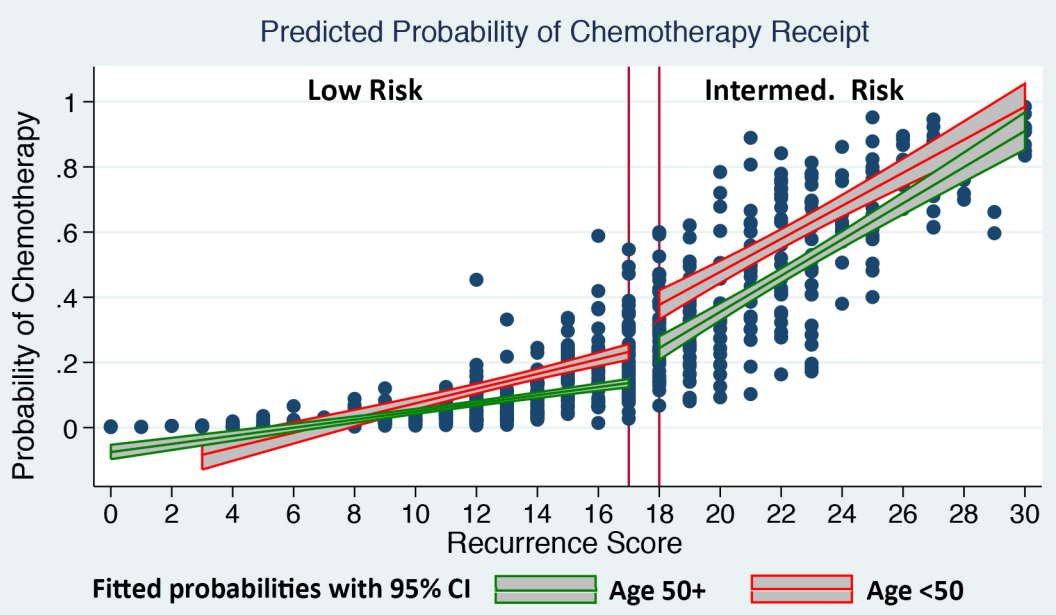
[#]Recurrence score recentered at score 17.5 (boundary between low and intermediate risks). Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Model 1 was also evaluated with the inclusion of the Charlson's index. The coefficient for Charlson's index was not significant. In its presence the coefficient for age was not modified in magnitude and direction but it became not significant, likely due to collinearity of information. As none of the other coefficients were affected and self-reported health status was included in the model, the Charlson's index was not retained in the analysis.

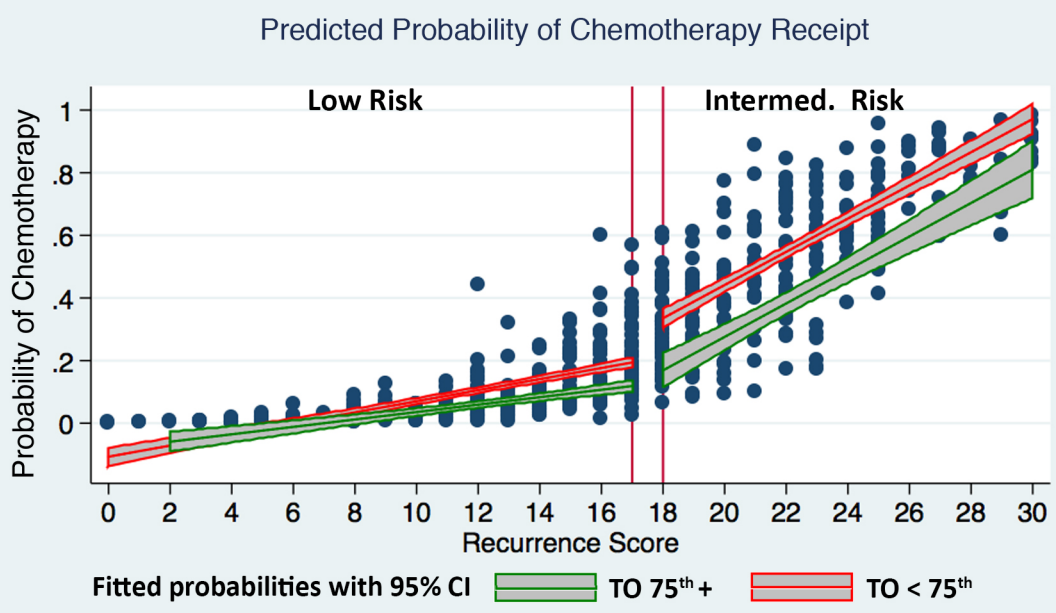
4.6 SUPPLEMENTAL MATERIAL

Figure 4.S1: Variations in the predicted probability of chemotherapy use for low–intermediate risk patients by age (A) and by opportunity cost of time (B)

A.



B.



The probability of receiving chemotherapy was predicted using the fixed parameters of the full model for multilevel logistic regression presented in Table 4.5. The plots feature the predicted probabilities for all patients at low and intermediate risks (grey dots), and the fitted values and 95% confidence intervals for

groups of interest after risk stratification (low vs. intermediate). A, Patients aged less than 50 (green, n=230), and 50 or older (red, n=417). B, Patients scoring at the 75th to 100th percentile for opportunity cost of time (scores ≥.7387; green, n=202), and patients scoring below the 75th percentile (score < .7387, red, n= 598). Non-overlapping 95% confidence intervals (in grey) indicate significant differences between groups. The vertical bars (red) mark the cutoffs between low risk (<18) and intermediate risk (18–30).

Table 4.S1: Comparison of the complete cases used in regression analysis and the cases with missing values among the patients at low and intermediate risk

Low and intermediate risk	All N=802	Complete cases N=647	Cases with missing values N=155	*P*
Age at test	**52 (7)**	**52 (7)**	**54 (7)**	**.005**
Charlson score	**1.85 (.99)**	**1.81 (.96)**	**1.99 (.94)**	**.004**
Health				**.002**
Excellent (ref.)	20%	**20%**	**19%**	
Very good	46%	**48%**	**33%**	
Good	29%	**26%**	**40%**	
Fair/poor	6%	**6%**	**8%**	
Risk Score	16 (6)	16 (6)	15 (6)	.442
Recurrence risk				.204
Low	61%	60%	66%	
Intermediate	39%	40%	34%	
Chemotherapy use	25%	26%	21%	.169
Race/Ethnicity				.080
White	62.6%	63.9%	56.7%	
Hispanic	12.1%	12.1%	12.0%	
Black	11.4%	9.9%	18%	
Asian	11.3%	11.3%	11.3%	
Other	2.6%	2.8%	2.5%	
≤ High school	12%	12%	14%	.436
Graduate school	**25%**	**28%**	**13%**	**< .001**
Income < $40,000	**11%**	**10%**	**16%**	**.037**
Income ≥ $150,000	**28%**	**31%**	**15%**	**< .001**
Lower health literacy	**4.4%**	**3.7%**	**7.4%**	**.046**
Language preferred	3.0%	2.6%	4.9%	.153
Communication	-.01 (1.00)	.01 (1.00)	-.09 (.98)	.281
Physician mistrust	.00 (1.00)	-.01 (.99)	.05 (1.04)	.507
Family support	.00 (.99)	.01 (.99)	-.01 (1.04)	.399
Time opportunity	.03 (1.00)	.01 (1.00)	.22 (1.01)	.123
Worry about work	.00 (1.00)	.01 (1.00)	-.10 (1.04)	.405
Rural residence	11%	12%	8%	.222
Year of treatment				.290
2009	12%	12%	11%	
2010	23%	23%	21%	
2011	30%	31%	26%	
2012	35%	34%	42%	
U.S. Census region				.064
Northeast (ref.)	**24%**	**24%**	**25%**	
North Central	**11%**	**11%**	**12%**	
South	**46%**	**45%**	**52%**	
West	**18%**	**20%**	**11%**	

Differences between the group of complete cases and the group of cases with missing values were tested using two-sided t-test for continuous variables, two-sided proportion tests for the indicator variables, and Pearson chi-square for the distribution of categorical variables.
P <.05 indicates significant differences between groups.

The percentage of missing values for each individual variable in the low-intermediate risk patients was at most 5%, except for income (7% missing), family support score (8%), and opportunity cost of time and influence of work (each, 10%).

Table 4.S2: Patient–physician communication and factors that may influence the chemotherapy decision

Characteristics	All Women n = 890†	Hispanic n = 108 (12.1%)	Black n = 112 (12.6%)	Asian n = 97 (10.9%)	White n = 549 (61.7%)	Other[1] n = 24 (2.7%)	*P*
Communication with physician							
Lower health literacy	41 (4.6%)	13 (12.0%)	3 (2.7%)	7 (7.2%)	17 (3.1%)	1 (4.2%)	**<.001**
Preference for language other than English	24 (2.7%)	14 (13.0%)	1 (.9%)	4 (4.1%)	3 (.6%)	1 (4.2%)	**<.001**
Communication [#]	.00 (1.00)	-.13 (.95)	.07 (.91)	.00 (.90)	.01 (1.05)	-.00 (.82)	.665
Physician mistrust[#]	.00 (1.00)	.06 (1.03)	.03 (.98)	.34 (1.07)	-.08 (.98)	.00 (.83)	**.007**
Factors that may influence the treatment decision							
Family support [#]	.00 (1.00)	.19 (.84)	-.32 (1.08)	-.01 (1.05)	.01 (1.00)	.39 (.72)	**.001**
Opportunity cost of time [#]	.00 (1.00)	.34 (.98)	.01 (1.06)	.40 (1.01)	-.14 (.95)	-.26 (1.09)	**<.001**
Worry about work [#]	.00 (1.00)	-.15 (1.03)	.39 (.87)	.11 (.93)	-.09 (1.01)	-.07 (1.04)	**<.001**

Continuous variables, mean (SD); categorical variables, frequencies (percent given by columns). Differences in means tested between groups using ANOVA and differences in distribution tested using Pearson's chi-square. Source: patient reported measures and summary scores obtained by principal component analysis. Less than 5% of the values are missing for each variable, except for the three summary scores for family support, opportunity cost of time and worry about work (9% missing each). [#] Greater scores indicate higher quality of communication, greater mistrust, greater level of support, greater opportunity cost of time or greater worry about work, respectively.

Race/ethnicity is based on self-reports recoded into 5 mutually exclusive categories; † race/ethnicity is unknown for 6 respondents; claims and laboratory data are missing for 2 respondents (0.2%). [1] Other: Native Hawaiian/Pacific Islander, American Indian/Alaska Native, or multiracial respondent who reported no identification with one group in particular.

Table 4.S3: Predicted marginal effects of race/ethnicity in the treatment decision

Predicted probability of receiving chemotherapy for low and intermediate-risk patients				
Race/Ethnicity	Mean probability	95% Conf. Interval	Mean difference with White	P
White	24.9	[21.4 28.4]	-	-
Hispanic	28.4	[20.2 36.5]	3.4	.453
Black	**37.6**	**[27.4 47.7]**	**12.6**	**.022**
Asian	21.9	[13.3 30.7]	-3.0	.540
Other	16.9	[4.0 29.8]	-8.1	.240

Mean predicted probabilities and differences are expressed in percentage points.

P < .05 indicates significant difference for patients of a racial/ethnic group compared to White patients of similar characteristics and adjusting for clustering by area of residence.

Variance estimation of the mean probability using Taylor series approximation applied to the fixed components of the full model using multilevel logistic regression. Odds ratio for the corresponding models are presented in Table 4.5.

CHAPTER 5

CONCLUSIONS, LIMITATIONS AND FUTURE RESEARCH

5.1 SUMMARY OF RESULTS

Personalized medicine is still at an early stage and new methods are needed to better understand how patient knowledge and preferences may influence treatment decision. This dissertation brings new knowledge to conceptualize treatment decisions guided by a genomic test.

First, the research identifies new pathways that help conceptualize the decision process from the patient perspective. We identified a first path between patient preferences and treatment decision on which risk perception intervenes and suppresses the effect of patient preferences (Chapter 2). A second path involves information exchange between patient and physician. We found a significant association of information exchange with the treatment decision of receiving chemotherapy, and this relationship is moderated by risk perception (Chapter 3).

Second, the research helps understand mechanisms by which new disparities in care may emerge, as both risk perception and information exchange are significantly associated with race and ethnicity. We examined variations in treatment decision by race and ethnicity in the same cohort, and found variations in the directions predicted by the model (Chapter 4). Variations in treatment decision were significant for women at intermediate risk for whom uncertainty remains about what may be the best treatment option. More specifically, we found significant variations by age, race, and reported opportunity cost of time. Those variations may be relate to differences in diagnosis and tumor stage, or, as the model supports, to differences in patient preferences, but it is also possible that they constitute a new source of health care disparities that would need to be addressed.

5.2 POLICY IMPLICATIONS

The dissertation has direct policy implications: 1) it identifies needs in methods and measures to better evaluate the communication about genomic test and its impact on medical care in a clinical setting; 2) it identifies actionable targets for the design of interventions, specifically, risk perception and information exchange; and 3) it provides new knowledge on potential disparities in care that may emerge from the use of genomic test.

5.2.1. Needs in measures and methods to assess the impact of genomic tests in clinical care

As mentioned above, the field of personalized medicine is still at an early stage. Translation into clinical care has been slow despite the rapid proliferation of genomic and genetic tests, in part due to the limited body of evidence for their clinical utility (Burke and Korngiebel, 2015). In 2011 a horizon scanning for genetic testing performed for the Agency for Healthcare Research and Quality (AHRQ) identified over 100 genetic and genomic tests related to cancer, a double in number compared to 2006 (Raman et al., 2011). In contrast, a systematic review of professional guidelines and recommendations identified 45 genomic tests with cancer-related applications, but only 50% of them receiving positive recommendations for use in practice (Chang, 2014 #1101). Discrepancies in recommendations between organizations were observed for several genomic tests (including for Onco*type* DX for breast cancer). Those differences may result from differences in evidence available at the time of evaluation, but also from differences in evaluation criteria (Burke and Korngiebel, 2015; Chang et al., 2014).

One implication of the study is the need to develop standardized measures for patient preferences and risk perception, and to use prospective design to record patient preferences and

risk perception before and after the treatment decision. This issue is not new, and is not limited to the personalized medicine, but it may be more critical for this emerging field still in need to demonstrate value within the health care system. The development of those measures should take in account the need for a rapid and accurate assessment in a clinical setting to be compatible with the recruitment of patients at an early stage of their treatment. Therefore, it should consider the emotional state of newly diagnosed patients during the collection of information. The development of those measures will be important to evaluate the clinical utility of genomic test in addition to more traditional outcomes, from treatment decision to prevention of disease recurrence.

A rapid assessment of patient eligibility at an early phase of their treatment may become feasible using electronic medical records, as it would eliminate delay required in processing claims. But it may be difficult to implement as electronic records systems are also at an early stage of implementation in many practices. Also, the lack of harmonization between systems may complicate the data collection. An important challenge in tracking the use of genomic and genetics tests is the paucity in unique identifiers for molecular tests in billing systems, and Oncotype DX may have been one of the few tests identified with a specific code during the time period of the study. Indeed, at the time of the study, Onco*type* DX was the most predominant genomic test for breast cancer on the market, and the CPT code "S3854 - Gene expression profiling panel for use in the management of breast cancer treatment" was de facto specific for Oncotype DX—among 1424 eligible participants for the study, only 24 were excluded because they had received a different genomic test in 2009-2012. However, the market is rapidly changing with the increasing diffusion of competitor tests, such as Mammaprint (Agendia, Amsterdam, The Netherlands) and Prosigna Breast Cancer Assay (Nanostring Technologies, Inc,

Seattle, WA). Those tests provide guidance for treatment decisions using different technologies and different patient classifications leading to different treatment recommendations. To avoid confusion among providers and patients, it is therefore essential to collect reliable and accurate information to evaluate their comparability, starting by identifying which test was ordered.

An important policy recommendation for the development of measure applied to personalized medicine is the development of unique and universal identifiers for genomic tests. A first step in this direction in 2011 was the establishment of the Molecular Diagnostic Services Program (MolDX) by Palmetto GBA, the carrier for Medicare in three states including California (Peabody et al., 2014). Under this initiative, a technology assessment is now required to show clinical utility of a test before it is approved for coverage (Peabody et al., 2014). Currently, over 150 molecular diagnostic tests are registered in MolDX, and approved for limited coverage by Medicare (Center for Medicare and Medicaid Services, 2015). A second initiative under the leadership of the American Medical Association was launched in 2014 with the development of Z-codes. The development of unique and universal identifiers for genomic tests will be an important step for the development of personalized medicine, as it will support the evaluation of their use in a real-world setting. The issue of documenting clinical value is important not only for the health care system and for the quality of care, but also for the economy as it is estimated that the share of personalized medicine will reach 5–10% of the entire pharmaceutical market within the next decade (Kalia, 2013).

5.2.2 Identification of potential intervention targets to improve decision-making using a genomic test

Taken together, the three papers in this dissertation provide findings to support the recommendation that interventions aiming to improve decision-making using a genomic test should include: 1) interventions targeting patients to better educate about disease risk and treatment options, and support an informed decision; and 2) interventions helping physicians in eliciting patient attitudes and preferences, and in engaging in a shared decision process. We offer that the new relationships identified here may help better understand decision-making in the case of uncertainty between different treatment options. It may also help improve the quality of care for more vulnerable populations by pointing to actionable points in the decision process. This is important as patients are asked to become more active participants in their medical treatment in the context of patient-centered care, and patient needs may vary.

Also, the findings suggest avenues for better tailoring the interventions towards the needs of specific groups. For instance, the finding that Hispanic women were more likely to perceive elevated level of risk, suggests that interventions towards Hispanic patients should include components helping patients to understand risk better and to reduce their misperception. In contrast, issues in information exchange that were more pronounced among African-American patients may be addressed by supporting patients in engaging more in the discussion about the test result, and in feeling empowered to ask questions.

5.2.3 Genomic Testing: a New Source of Disparities in Breast Cancer Care?

Despite an undeniable success in the fight against breast cancer, differences in outcomes are still observed between different racial/ethnic groups (Li et al., 2003). In 2007, African-American women were 39% more likely to die from breast cancer than White women, whereas breast cancer incidence is higher among White women (American Cancer Society, 2011). Hispanic and Native American women also have poorer survival rates than White women, in contrast to Asian and Pacific Islanders women who do not (Li, 2005; Li et al., 2003). Disparities in outcomes exist among patients diagnosed at early-stage, notably with worse survival observed for Black Women compared to Whites (Berz et al., 2009), and may relate to differences in tumor stage at diagnosis but also in differences in quality of care.

Disparities in breast cancer outcomes are multifactorial, with an accumulation of differences at all stages of the cancer care continuum, from screening to treatment (Li, 2005; Li et al., 2003; Murphy et al., 2010; Wheeler et al., 2013). Factors contributing to disparities include socioeconomic factors that create barriers to preventive services and delay access to care (Gerend and Pai, 2008; Grann et al., 2006; Mandelblatt et al., 1995; Shariff-Marco et al., 2014); social factors that are significant health determinants (Sprague et al., 2011; Thomson et al., 2001); perceived racism and discrimination that may significantly impair health through elevated stress, poor access to care, and distrust of the health care system (D'Anna et al., 2010); and differences in tumor characteristics, including a higher prevalence of triple-negative breast cancers with poorer prognosis among Black women (American Cancer Society, 2011).

Disparities in care and outcomes persist even after controlling for clinical factors and access to care. More specifically, disparities in the treatment of early-stage breast cancer include lower rate of definitive local therapy (i.e., lower rate of mastectomy, or failure to receive radiation

therapy after breast-conserving surgery; Freedman et al., 2009; Joslyn, 2002; Sail et al., 2012), and failure to initiate and complete hormonal therapy (Livaudais et al., 2012; Reeder-Hayes et al., 2014; Short et al., 2010). While data collected in 1990-2005 showed important disparities in chemotherapy use (Bickell et al., 2006; Hershman et al., 2005; Sail et al., 2012), more recent studies suggest that important progress has been made towards a more equal access to chemotherapy (Neugut et al., 2012; Silva et al., 2013).

Disparities in treatment have been associated with differences in guideline-concordance (Wu et al., 2012), patient socioeconomic status (Wheeler et al., 2013), and provider factors (Keating et al., 2009; Mojica et al., 2007a; Murphy et al., 2010). The addition of genomic testing to the oncologist toolbox may add a new source of disparities in breast cancer care. Already, several studies have detected disparities in genomic test ordering (Haas et al., 2011b; Hassett et al., 2012; Lund et al., 2012). Notably, Black women were half as likely as White women to have the test ordered, despite their eligibility (Lund et al., 2012). A study of New York City hospitals found significant disparities in ordering at municipal hospitals but not at tertiary hospitals in 2006–2009, suggesting that volume of ordering and system factors may be influential (Guth et al., 2013). In contrast, no differences in ordering by race and ethnicity were detected in a small single-center study (DeFrank et al., 2013b), and in a large Medicare population (Dinan et al., 2015).

But ordering is only the first step in the use of genomic testing, and the present studies bring new knowledge on how patients perceive the use of genomic test in their treatment, and how communication may vary with race and ethnicity. While women eligible for the genomic test are predominantly White women due to the higher incidence of the diagnosis in this population, it is now more than ever relevant to document the preferences and attitudes of diverse patient

populations. First, it is a matter of equity to ensure that all patients benefit equally from the progress in quality of care brought by personalized medicine. Second, recent epidemiology data found that the incidence of ER+ breast cancer was increasing among non-elderly Black and Hispanic women (Desantis et al., 2014). Finally, a shift in diagnosis towards early-stage breast cancers in minority population is likely to occur with increased insurance coverage and access to screening under the Affordable Care Act—insurance status is a strong determinant for early diagnosis (Coburn et al., 2008; Levy et al., 2012; Sabik et al., 2015; Ward et al., 2010).

Finally, there is still paucity of data regarding health outcomes following the use of a genomic test in diverse patient populations, and more evidence may needed to fully validate the use of genomic test in diverse populations (Odierna et al., 2011). However, the application of Onco*type* DX is limited to hormonal receptor-positive tumors, and one can argue that from a biological point of view, the panel of genes examined by the test (mostly biomarkers for cell proliferation and tumor invasiveness) is likely to be relevant for all patient independently of their genetic ancestry. The case would likely be different for a genomic test for "triple negative" breast cancers that have a biology distinct from hormone receptor-positive tumors, and a higher incidence among African American women compared to White women (American Cancer Society, 2011).

In conclusion, it is essential to identify factors that may impact the use of the genomic tests in decision-making, and research efforts should serve the dual goal of improving the quality of care using those tests, and also of maximizing its benefits for diverse populations of patients.

5.5 FUTURE RESEARCH

The findings of the studies point to several directions for future studies using breast cancer treatment as a model for the study of decision-making using genomic tests.

First, the research presented here examined the patient perspective on the use of the genomic test in the treatment decision. We found that most patients received excellent quality of care based on the concordance with the guidelines, despite 20% of them not recalling, or not knowing, the result. Therefore it is important to determine if the lack of knowledge has any effect on the quality of life and satisfaction of those patients. Qualitative studies including key informant interviews, may help provide supplemental information on those more subjective outcomes of the treatment decision. In parallel, studies should fill the gap in knowledge on the physician perspective. In particular, information is needed on how physicians use the test to engage patients in treatment decisions. Also, studies should explore their perspective on the utility of communicating about the test result with their patients compared to other clinical information available. Finally, it needs to be determined how factors, such as race and ethnicity, may impact physician communication about the test results.

Second, our conceptual framework provides a blueprint for future studies with a prospective design. In particular, it will be important to document patient preferences and risk perception before and after communication of the test result, and to document the information exchange occurring at the time of the communication about results and at the time of the treatment decision. As mentioned above, another important issue is to determine if patient knowledge and patient participation in the treatment decision using the genomic test have an effect on the quality of life and satisfaction of patients following the treatment decision.

Finally, another research direction relates to the use of the hormonal therapy among women who have received the test. In the present study no data was available on patient use of hormonal therapy. This is an important issue as the recurrence risk predicted by the genomic test is conditional on the patient completing this part of the treatment, and long-term hormonal therapy adherence may be difficult for patients. Complementing claims data with data from pharmacies may help evaluate the magnitude of the problem and determine if women who received the test are more likely to adhere to hormonal therapy that those who were not tested. Also, the prospective studies proposed above should combine patient reports with pharmacy records to document the use of hormonal therapy over time.

Personalized medicine is still at an early stage of its diffusion in the clinical setting, and now is the right time to develop measures and methods that will help ensure its utility in clinical care and fulfill the needs of patients and physicians. The dissertation illustrates a patient-centered approach using the model of a genomic test in breast cancer care. We expanded on existing conceptual frameworks by defining new pathways in the treatment decision process; importantly, those pathways involved factors that may be changed by interventions. Results of this type of research need to be shared with both physicians and patients to improve quality of care and communication. Finally the field cannot move forward without receiving feedback from patients and their providers on what matters most in practice to ensure that the use of personalized medicine and genomic tests brings added value to health care.

APPENDIX

The research uses data collected in a national survey of privately insured women aged less than 65 years old and who received a claim for Onco*type* DX during their treatment for early-stage ER+ LN– breast cancer. This section describes the survey design, sampling strategy, and data collection.

A1. Design of the questionnaire

The questionnaire explored patient perspective on the following domains: role in decision-making; perception of risk of recurrence; factors that might support or detract from initiating chemotherapy (family support, time opportunity, perception of risk and side-effects, value of the treatment); quality of the interaction with the physician (communication, mistrust, perception of unfair treatment); knowledge about the recurrence risk test and its use in treatment decision.

Whenever possible, questions published in high-quality studies were adapted to the specifics of the survey. The survey was formatted with attention to limiting respondent's burden and keeping readability close to the 8th grade-level. The questionnaire was reviewed for content and format by a medical oncologist and a survey methodologist, and a pre-test was performed on 3 patients with early-stage ER+ LN– breast cancer, who had received the test. The survey was provided in English only.

A2. Power calculation and sampling strategy

Using data from a similar cohort, it was estimated that a sample of 300 White and 300 non-White respondents would be sufficient to detect a 17% difference in the use of chemotherapy with 90% statistical power, and that subgroups of 100 respondents would result in 80% power. Based on 2009 data, only 20% of eligible patients were predicted to be non-White, which led to

oversampling that group. As differential response rates had been reported for White and non-White in the literature (60% versus 40%, respectively; Kelly et al., 2010) a conservative response rate of 40% was assumed and led to an estimate of 750 invitations per group to achieve the target sample.

The sampling strategy required identifying if eligible participants were White or non-White based on information from health plans. As collection of information on race/ethnicity is not mandatory for private insurers, self-reported race/ethnicity was available for only 46% of members receiving a claim between January 2009 and November 2012. Additional information on race/ethnicity was collected for 8.6% of the eligible sample from other sources (including the Member History Registry, and Healthcare Effectiveness Data and Information Set (HEDIS) measures). In the absence of information (45% of all eligible), minority status was predicted using the Bayesian Improved Surname Geocoding (BISG) method that combines last name and geocoding analysis (Elliott et al., 2008). This method was shown to improve the prediction of race/ethnicity compared to the analysis of geocoding, or surname only (Fiscella and Fremont, 2006). The misclassification rate was evaluated later by comparing the minority status used in sampling with the self-reported race/ethnicity from the survey.

A3. Mailing strategy

Following Dillman's mailed survey method (Dillman, 1978), eligible participants (n=1426) were informed of the survey by an invitation letter from the health plan. A week later a survey package was sent with a cover letter from the health plan, a study information sheet, the survey questionnaire with a unique study identifier, a prepaid return envelope, and a $10 incentive. A reminder postcard was sent to all participants two weeks later, followed by a second copy of the survey package to the non-respondents two weeks after. Participants were given the option to

take the survey online using Lime Survey (Hamburg, Germany). Informed consent was self-administered by submitting the completed questionnaire by mail or online; participants also authorized the research team to receive treatment information from the health plan, and test results from the laboratory performing the genomic test.

A4. Data collection

Data entry of the mailed responses was performed in duplicate using the Lime Survey platform. Differences between duplicate entries were resolved by review of the questionnaire forms. Survey data were linked to individual respondent information communicated by the health plan: age at the time of the test, indication of comorbidities, health plan type, and geographic information (ZIP codes recoded into 2011 U.S. Census regions, and Core Based Statistical Areas), as well as confirmatory information about year of testing, and use of chemotherapy, radiation, and surgery. The dataset was complemented by laboratory results, including the actual risk score on a scale of 0–100, confirmatory clinical information (ER, PR and Her2 status), and geographic information for the physician ordering the test (city and state). To protect participant privacy and confidentiality, all information from claims and laboratory results for the respondents were collected by the health plan, and the research team received only de-identified information that was linked to the survey responses using a study identification number featured on the questionnaire.

Aggregated information on non-respondents were obtained from the health plan to compare demographic characteristics between respondents and non-respondents that may indicate a non-response bias; aggregated data on non-respondents were limited to age distribution, year of test claim, U.S. Census region, health plan type, and minority status used in the sampling.

A5. Survey sample

4,410 eligible patients were identified among 6,650 members receiving a claim for a recurrence risk test between January 2009 and November 2012 (Figure A1). All 728 members identified as non-White were included, and 728 women were randomly selected among the 3,682 members identified as White, after stratification by year of diagnosis, age (<50 years, and 50–64), population density (rural/urban/suburban) and U.S. Census region to balance the groups. 24 potential participants were further excluded for receiving a recurrence test other than Onco*type* DX, and 8 because of an invalid mailing address, resulting in 1424 survey invitations.

The survey was launched on August 2nd 2013, and closed on December 31st 2013. Target goals were exceeded with a total of 896 responses and a high response rate of 63%. As anticipated, the response rate was higher for White than non-White women (77% versus 48%). Online responses represented only 8% of all responses.

Demographic characteristics of respondents and non-respondents were compared to assess if there was a nonresponse bias (Table A1). Respondents tended to be slightly older, more frequently White, and had more often reported on their race/ethnicity to the health plan, compared to non-respondents (all, $P < .05$). No differences in distribution were found between the two groups by year of test claims, or by type of health plan (POS, HMO, or PPO); in contrast, significant geographic variations were identified, with respondents living more frequently in the North Central and West regions, and non-respondents living more frequently in the South region.

Self-report on race/ethnicity in the survey (available for 890 respondents out of 896) was compared to the information used in sampling to assess misclassification. Only 9% of the non-White respondents were misclassified as White, and the rate was higher for White (20%).

Misclassification rates resulting from indirect estimation were similar to those reported in a validation study performed on a similar insured population (Elliott et al., 2009).

A5. Geographic distribution of the patients

Respondents resided in 176 CBSA (Core-Based Statistical Areas, U.S. Census 2010, equivalent to metropolitan areas of 10,000+ inhabitants) in 45 states. Clusters of patients by CBSA tended to be small, with on average 4.6 participants (SD 8.0), and only 25 areas regrouped more than 10 participants (Figure A2). While the participants more frequently resided in the West and Northeast regions, the areas most represented at the CBSA level were New York, NY (n=57); Houston, TX (n=55); Atlanta, GA (n=52); Philadelphia, PA (n=44); and Washington, DC (n=38) with these four cities accounting for 27% of the sample.

Information on the provider ordering the test was obtained for each patient from the laboratory records, and included city and state of the provider. The clustering of the patients by ordering providers was very granular with 680 physicians in 353 cities and 45 states, with a physician seeing on average 1.3 respondents (SD 0.9)—only six physicians ordered the test for more than 5 patients in the sample (Figure A3). Stratification by city within state resulted in 363 ordering sites, with an average of 2.5 patients per sites (Figure A3). Only 10 sites regrouped more than 10 patients—including Houston, TX (44); New York, NY (35); Atlanta, GA (34); Philadelphia, PA (23); and Washington, DC (23), together accounting for 18% of the sample. Most patients received the test order in their state of residence, and only 79 patients had the test ordered in a different state. So, overall the distributions of patients by site of residence and by site of care (city within state) were similar.

A6. Supplemental information on the measures

A6.1 Race/ethnicity

Race/ethnicity was self-reported in the survey based on the 1997 Office of Management and Budget (OMB) standards on race and ethnicity. Respondents were first asked to identify as Hispanic/Latina or non-Hispanic/Latina, and then to choose one or several race categories from: White/Caucasian, Black/African American, Asian American, Native Hawaiian/Pacific Islander, American Indian/Alaska Native, and Other. Multiracial respondents were further asked if they identified more with one race, and which one. If a preference for one race was expressed, the respondent was assigned to that group. Information was reclassified into five mutually exclusive categories: Hispanic, Black, Asian, White and Other (regrouping Native Hawaiian/Pacific Islander, American Indian/Alaska Native, and multiracial with no preferred identification with one race).

A6.2 Summary scores for quality of communication, physician mistrust, family support, opportunity cost of time, and worry about work

Summary scores were extracted from survey items by Principal Component Analysis (PCA) with a varimax rotation, and factors were retained if the eigenvalue was greater than 1. All scores were calculated so that the mean score was 0, and the standard deviation was 1.

Quality of communication with the physician is a summary score summarizing the rating of patient-physician communication (higher positive scores indicates better rating), and is based on 3 items for positive aspect of communication with the physician (listens carefully, encourages asking questions, understands background and values). Items used in PCA were on a 4-point Likert scale, and some items were recoded so that they would have the same direction before

PCA. The corresponding questions in the survey were adapted from Doescher and colleagues (2000) and from the 2001 Commonwealth Fund Survey on Disparities in Quality of Healthcare (Commonwealth Fund, 2001).

Physician mistrust is a score summarizing the patient mistrust of physician (higher indicates stronger mistrust), and is extracted by PCA from 4 self-reported items evaluating physician mistrust (trust that medical needs are put above all else [reverse coded], unnecessary tests/procedures, decisions influenced by insurance, doctor looks down on me). The items used were also adapted from Doescher and colleagues (2000) and from the 2001 Commonwealth Fund Survey on Disparities in Quality of Healthcare (Commonwealth Fund, 2001).

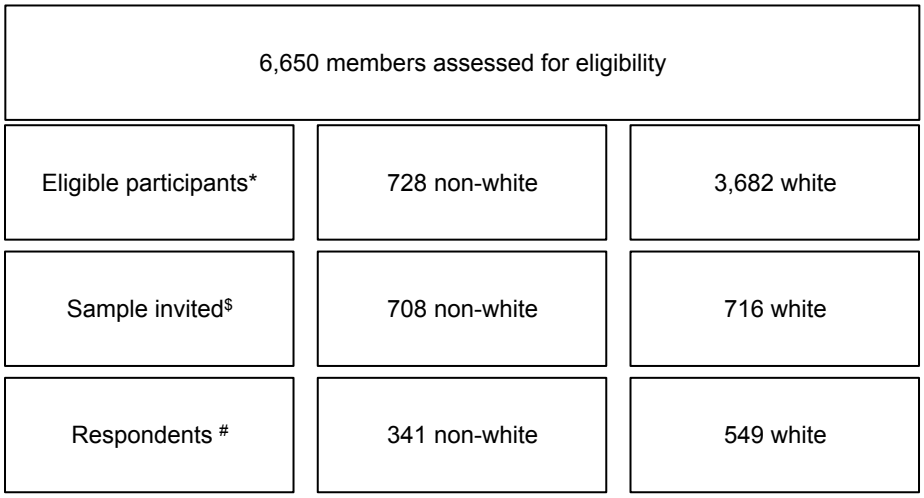
A score for *family support* (higher indicates stronger support) was produced using 7 attributes relevant to family support; the loading was obtained predominantly on items relevant to: marital status, family participation in medical decision, family present during doctor visit, family help in transportation, family provides emotional strength.

The score for *opportunity cost of time* and the score for *worry about work* were based on 8 items relevant to barriers influencing the decision of receiving chemotherapy in a survey question adapted from Degner and colleagues (1997a). The score for *opportunity cost of time* has a strong loading for burden on activities and family, time-off and work, traveling time to medical center. The score for *worry about work* was related more specifically to the burden of chemotherapy related to taking time off from work (self and family).

The validity of the summary scores was evaluated by looking at the correlation of the individual items with the summary score. The range of the correlation coefficients with their associated items were for *quality of communication*: 0.72-0.80; *mistrust*: 0.52-0.72; *family support*: correlation 0.53 - 0.79; *opportunity cost of time*: correlation 0.57 – 0.80; and *worry about work*: correlation 0.48-.90.

A7. Figures and Tables for the Appendix

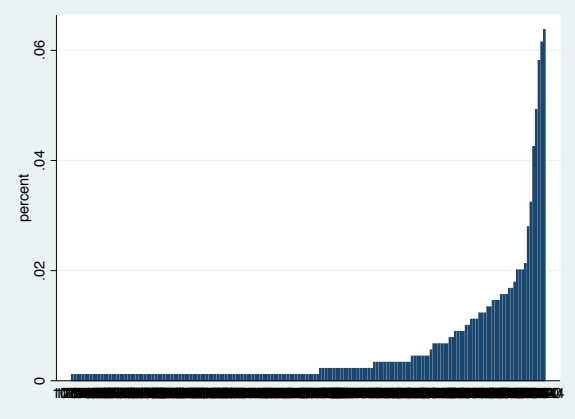
Figure A1: Sampling of non-elderly breast cancer patients receiving a claim for the genomic test



Eligibility was assessed for all female members aged less than 65 receiving a claim for the test, and enrolled for at least three months before and six months after the date of the claim.

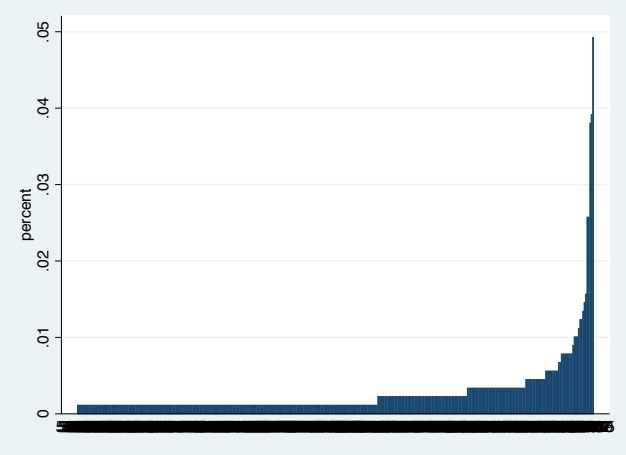
* Ineligibility reasons (non-exclusive) included: member not enrolled at the time of the survey (n= 1776), previous history of breast cancer or metastatic disease (n=812), or reported death (n=6). $ Exclusions from the sample included invalid postal address (n=8), and receiving a test other than Oncotype DX (n=24). # Out of 896 respondents, 6 did not report on race/ethnicity, and 2 online respondents were missing a study identification number preventing linkage with claims and laboratory records. Non-respondents included 16 postal returns, and 5 actively declined entering the study.

Figure A2: Histogram for the distribution of the patients by area of residence (CBSA within states)



x axis = individual cluster= CSBA within states; y axis= Percent of Participants in that cluster
CBSA are equivalent to metropolitan areas of 10,000+ residents.

Figure A3: Histogram for the distribution of the patients by site of test ordering (city within state).



x axis = individual cluster= city within states; y axis= Percent of Participants in that cluster

Table A1: Comparison of demographic characteristics of the survey respondents and non-respondents

	Invited Eligible n = 1424	**Respondents n = 894***	**Non-respondents[$] N = 530**	***P***
Age at time of the survey (year)	53.3 (7.3)	53.6 (6.9)	52.7 (7.8)	**0.024**
Aged 35-49 (%)	414 (29.1%)	233 (26.1%)	181 (34.2%)	**0.001**
Aged 50-65 (%)	991 (69.6%)	652 (72.9%)	339 (64.0%)	**<0.001**
Minority status **				**0.007**
White	716 (50.3%)	474 (53.0%)	242 (45.7%)	
Non-White	708 (49.7%)	420 (47.0%)	288 (54.3%)	
Self-reported race/ethnicity[#]	751 (52.7%)	494 (55.3%)	257 (48.5%)	**0.013**
Health Plan types				0.662
HMO	165 (11.6%)	102 (11.4%)	63 (11.9%)	
PPO/Indemnity	156 (11%)	90 (10.0%)	66 (12.4%)	
POS/Managed Choice	1103 (77.5%)	702 (78.5%)	401 (75.7%)	
U.S. Census regions				**0.001**
North Central	141 (9.9%)	100 (11.2%)	41 (7.7%)	
Northeast	361 (25.4%)	205 (22.9%)	156 (29.4%)	
South	697 (48.9%)	430 (48.1%)	267 (50.4%)	
West	225 (15.8%)	159 (17.8%)	66 (12.5%)	
Year of test claim				0.762
2009	182 (12.8%)	115 (12.9%)	67 (12.6%)	
2010	320 (22.5%)	197 (22.0%)	123 (23.2%)	
2011	412 (28.9%)	267 (29.9%)	145 (27.4%)	
2012	510 (35.8%)	315 (35.2%)	195 (36.8%)	

Continuous variables, mean (SD); categorical variables, frequencies (percent given by columns). Differences between respondents and non-respondents were tested using t-test for means, and Pearson's chi-square for distribution, all at alpha=.05.

* 896 women responded to the survey but information from claims is missing for 2 online respondents who did not provide a study identification number.

* Information available from the health plan and used in sampling (self-report or after imputation)

[#] % Eligible members who had self-reported information available in the health plan database

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