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Understanding How Multi-Level Factors Influence Cancer Clinical Trial Enrollment Decisions By Patients Living In Higher Disadvantaged Areas

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UNDERSTANDING HOW MULTI-LEVEL FACTORS INFLUENCE CANCER CLINICAL TRIAL ENROLLMENT DECISIONS BY PATIENTS LIVING IN HIGHER DISADVANTAGED AREAS

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EPIDEMIOLOGY

ABSTRACT

Cancer clinical trials offer current patients with cancer new treatment and novel interventions to treat their cancer, while advancing the care of future patients. Clinical trials test new drugs against the standard of care to determine drug efficacy and safety. There are many groups of patients who are either unrepresented or underrepresented in cancer clinical trials and there is a plethora of reasons they are not represented. One underrepresented population of interest is patients with cancer who live in highly disadvantaged neighborhoods. Previous research found that when compared to patients who live in areas of lower disadvantage, patients living in areas of higher disadvantage had similar odds of being interested, eligible, and offered to participate in a clinical trial; however, they had 3.4 times the odds of declining enrollment when offered to participate. Little is known as to why these patients are underrepresented. Furthermore, breast cancer is an ideal setting to understand underrepresentation as it is the second most common cancer diagnosis in the United States and is one of the cancer types with the largest number of Food & Drug Administration-approved drugs. To better understand the issue of trial underrepresentation from a multi-level perspective, we will, first, evaluate the association between county-level demographics and the availability of National Cancer Institute (NCI)-designated and NCI Community Oncology Research Program sites as access to these sites serve as proxies for available clinical trials. Secondly, to understand systems-

level barriers and facilitators to trial participation, we will estimate the association between area deprivation and willingness to participate in a future breast cancer clinical trial that has undergone trial modifications. Lastly, we will utilize Structural Equation Modeling to understand which patient-level factor is the greatest contributor to participation in a breast cancer clinical trial using a sample of patients who are socioeconomically vulnerable. This will include attitudes toward and knowledge of clinical trials along with the factors that comprise area deprivation, including education level, annual household income, and employment status. Findings from these analyses will inform the development of future interventions to increase enrollment in cancer clinical trials among vulnerable patients.

Keywords: cancer clinical trials, breast cancer, area deprivation, attitudes toward trials, trial modifications, access to care

DEDICATION

To God’s perfect plan which led me here.

“Oh give thanks to the Lord, for He is good, for His steadfast love endures forever!”

Psalm 107:1

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INTRODUCTION

Cancer clinical trials

Cancer clinical trials are randomized controlled trials that involve the testing of a new drug or novel intervention to find new and better ways to prevent, screen, treat, or support patients with cancer.[1] Clinical trials testing cancer treatment, known as therapeutic trials, specifically aim at testing new drugs in patients with cancer to determine their efficacy, including potential side effects, recurrence or progression of tumor, and survival outcomes, against standard-of-care treatments.[2,3] Previous literature has found that individuals not included in cancer clinical trials face worse outcomes (i.e., disability, disease, death).[4,5]

Lack of representation in cancer clinical trials

Patients who participate in cancer clinical trials benefit from having access to novel treatments and increased interaction with their oncology providers.[6,7] However, there are key groups of patients who are unrepresented, underrepresented, and well represented in clinical trials. One reason patients are unrepresented in trials is due to the plethora of inclusion and exclusion criteria[8] including lab abnormalities and comorbidities. Furthermore, eligibility criteria can include stage, subtype, or genetic mutations of the particular cancer.[9] Additionally, patients older than 69 years are underrepresented, which may be due to lack of interest in participating, age-related

comorbidities excluding participation, or being excluded entirely due to age.[10,11] Black, Indigenous, or People of Color (BIPOC) are underrepresented for multiple reasons, one being historical medical mistreatment and current policies that are rooted in systemic racism.[12,13] Black or African American patients often have more comorbidities than White patients, thus furthering their underrepresentation in clinical trials.[14,15] Patients living in rural or disadvantaged areas are underrepresented in clinical trials due to transportation and access barriers.[16,17] Transportation issues can include vehicle access, gas affordability, and distance to hospitals, thus further limiting their access to hospitals which offer cancer clinical trials.[18] Patients who live further away or with limited access more often present with later stages of cancer and experience cancer care delays, which has a negative effect on their treatment outcomes and overall survival.[19] Therefore, patients who are well represented in cancer clinical trials are typically White and within the ages of 45-69 years. It is important to note that all individuals experience intersectionality (definition: "the interconnected nature of social categorizations")[20] and therefore, depending on which social identities patients identify with, it can make participating in a cancer clinical trial challenging. To optimize quality and equitable cancer care, all patient populations should be represented in cancer clinical trials.

Importance of breast cancer clinical trials

As seen in cancer clinical trials generally, patients who are BIPOC, older, and reside in higher disadvantaged areas are underrepresented in breast cancer clinical trials. Breast cancer is an ideal setting to understand underrepresentation within clinical trials because breast cancer is the second most common cancer diagnosis, after skin cancer.

According to the National Cancer Institute (NCI), breast cancer represents 15% of all new cancer cases within the United States.[21] Additionally, research from 2017 found that breast cancer was one the cancer types with the largest number of drugs approved by the Food & Drug Administration, with 27 drugs, after leukemia with 40 and lymphoma with 28 drugs.[22] Furthermore, in the past decade, there has been an increase in the development of breast cancer treatment drugs, including immunotherapies and targeted therapies.[23-25] Therefore, representative therapeutic trials of breast cancer drugs are important to ensure drug efficacy and safety for all patients with this common cancer.

Conceptual models driving my dissertation

To understand ways to increase participation in cancer clinical trials among underrepresented patient populations, a multi-level approach is necessary. My dissertation is guided by two adapted conceptual models; they involve multiple levels that influence a patient's ability to enroll onto a cancer clinical trial. The first is built upon two conceptual models by Unger and Ford (Figure 1).[26-28] This conceptual model shows the pathway to clinical trial enrollment from the provider or systems perspective alongside the patient perspective. First, the trial must be available at the given hospital and the provider must be aware of its availability to be able to assess patient eligibility and offer the trial to the patient. From the patient perspective, there could be many barriers or facilitators for either declining or enrolling onto a trial which may include access, awareness, attitudes, social determinants of health, etc. Prior to declining or enrolling onto a trial, the provider and patient discuss the risks and benefits to the specific trial before the patient makes the decision.

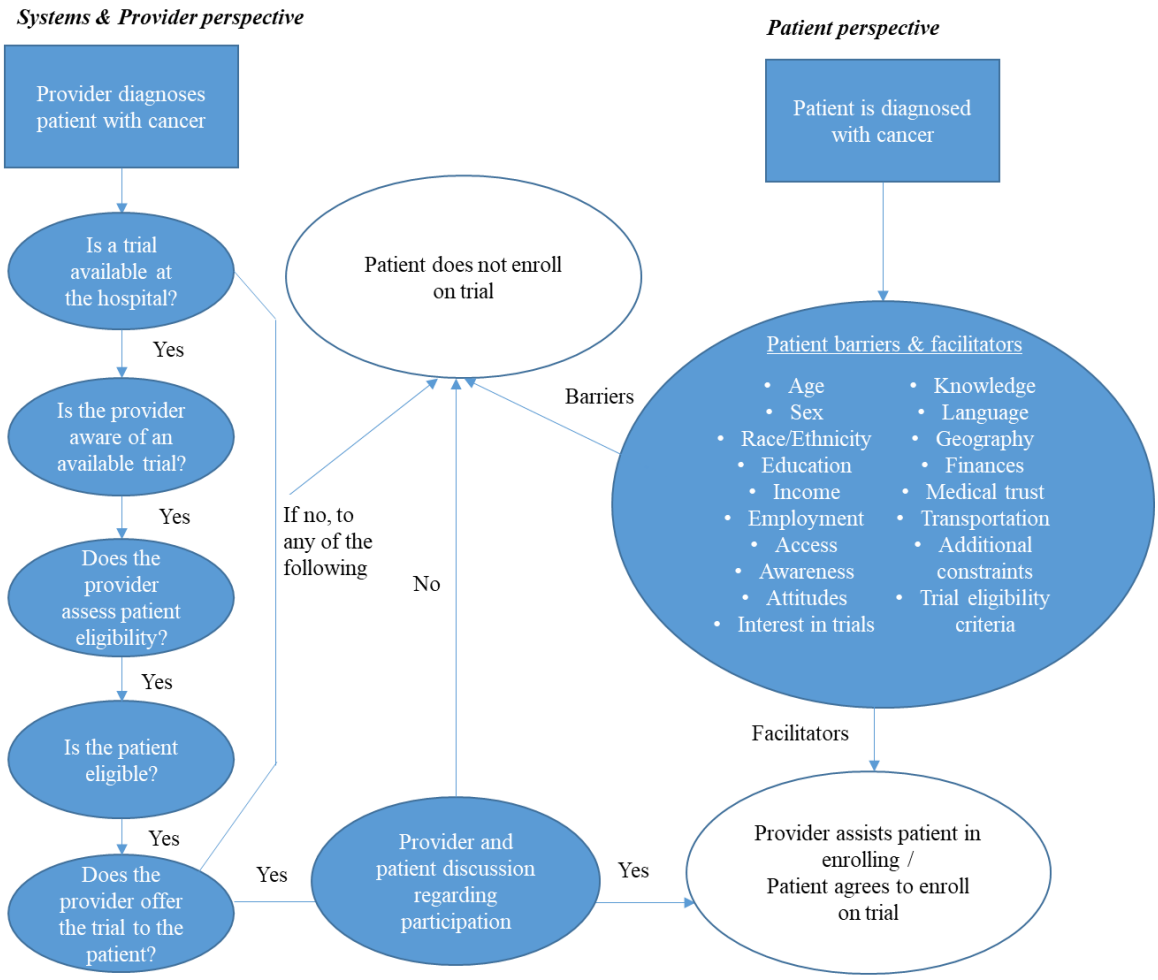

Figure 1. Conceptual model adapted from Unger and Ford.

For my second conceptual model, I adapted Taplin's conceptual model that depicts the multilevel influences on the cancer care continuum (Figure 2).[29] Talpin and colleagues' conceptual model involve seven different levels: national, state, community, hospital, provider, caregiver, and patient. Within each level, there are various factors including policy, insurance coverage, access, staffing, support systems, and individual level demographics and preferences which can affect the improvement of quality cancer care. I decided to focus on the county, systems, and patient levels for my dissertation as

these are important levels to intervene on to increase representation in cancer clinical trials.

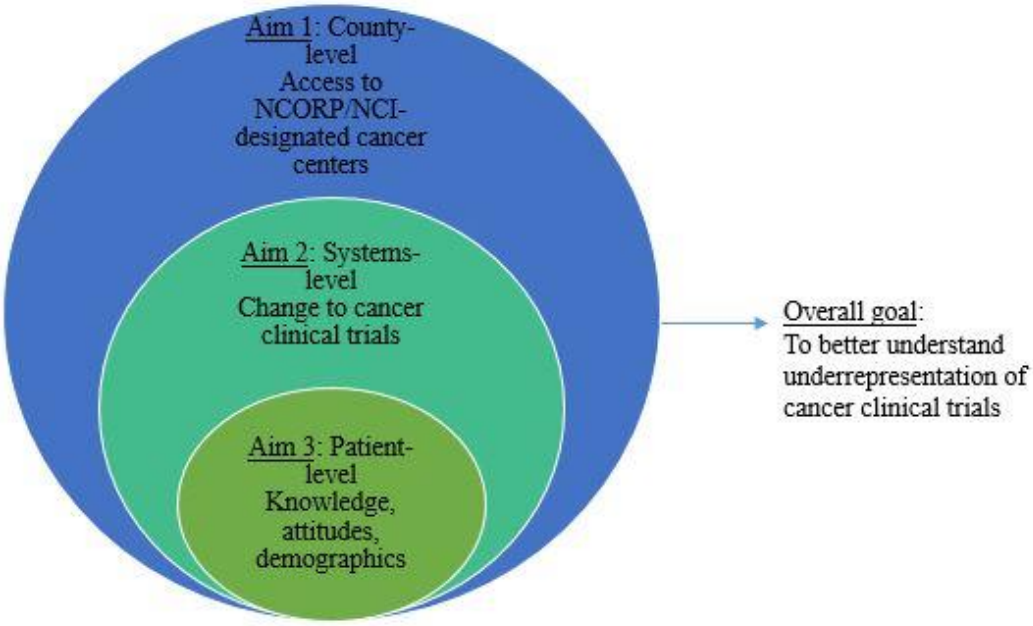

Figure 2. Conceptual model adapted from Taplin.

Geographical barriers to clinical trial participation

The initial step in the pathway to clinical trial enrollment is that the hospital within a geographical area has the resources and infrastructure to conduct cancer clinical trials, and that it facilitates trial participation among patients. Thus, it is imperative to investigate how the health care system can adapt to increase cancer clinical trial participation, including the ability for patients to access them and to be able to offer trials. One way in which the healthcare system has tried to increase trial participation is through the creation of the NCI Community Oncology Research Program (NCORP). Hospitals that are NCORP sites have access to resources to conduct trials and patients who live within travel distance to NCORP sites have access to clinical trials, as well.

However, little is known regarding the demographics of patient populations within the geographical area of NCORP site locations.

Neighborhood-level barriers

Patients commonly underrepresented in cancer clinical trials are individuals who live in highly disadvantaged neighborhoods. Neighborhood or area disadvantage is often defined by the housing quality, proximity of access to quality food or healthcare, crime, and walkability of the neighborhood, as well as generation education level, household income, and employment status of residents.[30] Previous research found that compared to patients living in areas of lower disadvantage, patients in areas of higher disadvantage had 3.4 times the odds of declining enrollment when offered to participate in cancer clinical trials, despite having similar odds of being interested, eligible, and offered.[27] However, there is little evidence why patients who live in higher disadvantaged areas are underrepresented in clinical trials. Therefore, my dissertation sought to add understanding and information to the extant literature with the goal of aiding in the development of targeted interventions to increase cancer clinical trial participation among individuals living in higher disadvantaged areas.

Healthcare systems-level barriers

In a systematic review, Ford and colleagues proposed a conceptual framework for the lack of participation among underrepresented patients.[28] They posit that reasons for individuals not being able to participate in a clinical trial are due not only to social determinants of health, but also systems-level barriers to participation. Ford's framework encompasses multiple levels that could influence a patient's participation in a clinical

trial, while highlighting that the clinical trial and/or healthcare system can cause barriers or facilitators to patient clinical trial participation, including the following: extensive eligibility criteria, provider awareness, and the hospital's ability to offer trials. During the COVID-19 pandemic, clinical trials had to adapt their procedures to retain participants and aid trial completion. These trial modifications included location changes, increased use of telemedicine, and more flexibility.[31,32] While it appears that sponsors and sites view trial modifications changes favorably, it is unknown if patient perspectives and willingness to participate in a modified trial differ by their neighborhood-level deprivation status and if these views are a driver for underrepresentation in cancer clinical trials.

Patient-level barriers

While area-level factors are important in understanding group characteristics, they may not represent an individual-level experience. As we seek to understand why patients who live in areas of higher disadvantage are underrepresented in clinical trials, evaluating the patient-level factors that comprise area deprivation is important. Previous literature has found that clinical trial non-participation at the patient-level stems from many factors, including health seeking-behavior, health literacy, education attainment, and income level.[16,33-36] However, these patient-level characteristics may not serve as the immediate drivers to participation. Sanbonmatsu and Fazio found that attitudes are often used in quick decisions and knowledge is used in a more deliberate decision-making process.[37] Furthermore, little is known about the interaction between attitudes, knowledge, and patient-level demographics and their associations with clinical trial participation.

Dissertation Purpose

The purpose of this dissertation is to better understand reasons for underrepresentation within cancer clinical trials, with a specific focus on individuals who live in areas of higher disadvantage or have limited socioeconomic resources.

Aim 1: Estimate associations between county-level demographics and access to NCORP and NCI-designated sites. We will use publicly available data from the NCI (to map location of NCI and NCORP sites), the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry's Social Vulnerability Index, and Health Resources & Services Administration's Area Health Resources Files. We will estimate the association between county-level demographics and access to both NCORP sites and NCI-designated Cancer Centers (as these are proxies for available clinical trials). We will assess the counties the NCORP and NCI sites are located in along with one concentric circle of counties surrounding the sites, as we hypothesis patients are likely to travel up to one county away for care.

Aim 2: Estimate the relationship between area-level disadvantage and willingness to participate given potential systems-level changes made to breast cancer clinical trials. We will use a diverse, nationwide sample of female patients with either early stage breast cancer within the past five year or advanced stage breast cancer at any point in time who have previously received case management or financial aid from the Patient Advocate Foundation. We will assess the association between both area deprivation and the willingness to participate in a breast cancer clinical trial that has undergone various

systems-level changes, including location, telemedicine, convenience, and opting out changes.

Aim 3: Evaluate which factor (patient-level education, income, employment, knowledge, & attitudes) is the greatest contributor to participation in a breast cancer clinical trial. To accomplish this aim, we will utilize Structural Equation Modeling using patient-reported data from the sample mentioned in Aim 2.

Research Contributions

The research contributions from these analyses will provide a better understanding of (1) where sites that conduct clinical trials are located and if they are accessible to the most vulnerable patients, (2) which clinical trial modifications are viewed most favorably by patients, particularly patients living in highly disadvantaged areas, and (3) which patient-level factors influence participation. Findings from this dissertation can inform policy by driving clinical trial sponsors to explore where they offer trials and how to make trial offerings more equitable to all patients with cancer. Additionally, findings may have an impact on how clinical trials are conducted in the future though the continuation of modified trials, which will hopefully mitigate access barriers. Finally, the findings will have the potential to lead to the development and testing of targeted interventions to increase patient participation in breast cancer clinical trials among patients who live in disadvantaged areas.

WHY LOCATION MATTERS: ASSOCIATIONS BETWEEN COUNTY-LEVEL DEMOGRAPHICS AND AVAILABILITY OF NATIONAL CANCER INSTITTUE COMMUNITY ONCOLOGY RESEARCH PROGRAM AND NATIONAL CANCER INSTITUTE SITES

by

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Abstract

Purpose: The majority of patients seek care at community oncology sites; however, most trials are available at National Cancer Institute (NCI)-designated sites. While the NCI National Cancer Oncology Research Program (NCORP) was designed to address this problem, little is known about the county-level demographics of NCORP site locations.

Methods: This cross-sectional analysis used publicly available data. Counties were determined as having at least one NCORP, one NCI, or both sites. To determine county-level demographics, we used data from the Centers for Disease Control and Prevention's Social Vulnerability Index. Health Resources and Services Administration's Area Health Resource Files were used to determine contiguous counties. We estimated risk ratios and 95% confidence intervals (CI) using modified Poisson regression models to evaluate the association between county-level demographics and availability of sites within singular and contiguous counties.

Results: Of the 3141 counties included, 14% had an NCORP, 2% had an NCI, and n=32 had both sites. Overall, NCORP and NCI sites were more often in metropolitan areas. Furthermore, as singular counties become more racially and ethnically diverse (one standard deviation increase), there was 1.22 times the probability of NCORP site availability (95% CI 1.10-1.36); however, there was a similar probability for contiguous counties. As counties become more vulnerable according to the socioeconomic status and household characteristics themes (one standard deviation increase), there was a 24% and 11% lower probability of NCORP site availability, respectively. NCI sites were located in more vulnerable counties.

Conclusion: While NCORP sites are reaching metropolitan counties and singular counties with racial diversity, they are not reaching rural nor socioeconomically vulnerable individuals. We suggest that NCORP sites deliberately partner with more community oncology and academic satellite sites to increase clinical trial participation and representation.

Background

Only 4% of the cancer patient population participated in trials held at community sites according to a 2021 publication by Unger and colleagues using data from the Commission on Cancer.[1] Furthermore, they found that approximately 20% of patients participated in trials held at National Cancer Institute (NCI)-designated sites. While this is likely because community sites often do not have the resources to conduct clinical trials, the majority of patients with cancer opt to receive cancer care at community oncology practices.[2,3] Health care systems need the ability to offer cancer clinical trials testing novel treatments and technologies to all patients with cancer as there are often health and well-being benefits to patients participating in clinical trials.[4]

The NCI National Cancer Oncology Research Program (NCORP) was designed to address this problem; NCORP's mission is to bring clinical trials to individuals in their own communities.[5] NCORP sites are located across the US (including Guam and Puerto Rico) with a total of seven Research Bases, 46 Community Sites (14 of those being Minority/Underserved Sites), and a total of 1029 participating hospitals (which may include multiple clinics within one overarching hospital system). Hospitals participating in the NCORP network have access to resources to successfully conduct clinical trials. Furthermore, the Minority/Underserved Sites were created to serve communities with a higher proportion of racially marginalized individuals. NCORP sites compliment the 63 NCI-designated cancer centers within the US (including cancer centers, comprehensive cancer centers, and basic laboratories), which conduct the majority of clinical trials.[6]

Despite goals of serving the broader population, according to an abstract by Nightingale et al, using responses from the 2022 Landscape Assessment survey, NCORP

sites reported that 79% of the population they serve are White patients.[7] This calls into question whether key populations are reached by NCORP and NCI sites. One such population is patients who live in rural or disadvantaged areas and face transportation issues (e.g., vehicle access, fuel/gas affordability, distance) and the inability to access hospitals not in their community, which may limit their access to novel treatment and technologies.[8] One postulated approach for increasing clinical trial participation for patients in these areas is the use of telehealth to mitigate barriers related to distance. The pandemic related increase in telemedicine usage within the US health care system[9] has potential to extend the reach of the NCORP sites, but internet access would be an important facilitator to patients participating in cancer clinical trials from community settings.

Questions remain about where NCORP and NCI sites are located, including area-level environmental, societal, logistical, and financial factors that may facilitate individuals' ability to access these sites. The objectives of our study are to understand the associations between county-level demographics and availability of both NCORP and NCI sites and to assess the potential for telehealth to extend the reach of these sites.

Methods

Study design and setting

This cross-sectional study utilized publicly available data of location of NCORP and NCI sites and county-level data for the US. The NCORP and NCI address information was downloaded in October 2022. Inclusion criteria included counties within the 50 states and

the District of Columbia. This study was exempt from Institutional Review Board approval due to the use of public data, which was downloaded from the internet.

Outcomes

Availability of NCORP and NCI sites: Individual counties were considered having access to an NCORP or NCI site if a site location was in the corresponding county. A secondary outcome was inclusion of an NCORP or NCI site for the corresponding county and its contiguous counties, as we hypothesized that the majority of patients would travel up to one county distance away to receive care. NCORP site locations were obtained from the NCORP website, which lists all NCORP sites and their addresses.[5] NCI sites were obtained from the NCI site county ShapeFile dataset.[10] Information on contiguous counties was available from the Health Resources and Services Administration's Area Health Resource Files (AHRF).[11] AHRF files contain county-level information for all counties within the US and data include population characteristics, various healthcare information, economics, and environment.

Exposures

County-level demographics and characteristics were abstracted from the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry's (CDC/ATSDR) Social Vulnerability Index (SVI).[12] The SVI uses 2020 US Census data to determine the communities' social vulnerability: factors that could weaken a community's ability to prevent loss, of both human and financial, following a disaster. Sixteen variables make up four themes: 1) socioeconomic status; 2) household

characteristics; 3) racial & ethnic minority status; and 4) housing type & transportation. Finally, the overall vulnerability theme combines all four themes. All themes are scored from 0 to 1, which are percentile rankings. For each theme, higher scores represent higher vulnerability.

Overall vulnerability theme: According to the CDC/ATSDR documentation, those counties with scores 0.90-1.0 are considered the highest vulnerable counties; 90% of counties are less vulnerable and 10% are more vulnerable. We used this logic to dichotomize counties. The following variables are included for each theme:

Socioeconomic status theme: Below 150% poverty, unemployed, housing cost burden, no high school diploma, and no health insurance.

Household characteristics theme: Aged 65 & older, aged 17 & younger, civilians with a disability, single-parent households, and English language proficiency.

Racial & ethnic minority status theme: Hispanic or Latino (of any race); Not Hispanic or Latino for Black and African American, American Indian and Alaska Native, Asian, Native Hawaiian and Other Pacific Islander, two or more races, other races.

Housing type & transportation theme: Multi-unit structures, mobile homes, crowding, no vehicle, and group quarters.

Additional county-level variables

We included 2013 Rural-Urban Continuum Codes (RUCC) from the AHRF dataset for each county. RUCC scores range from 1-9 with scores 1-3 representing metropolitan areas, 4-6 representing suburban areas, and scores 7-9 representing rural areas.[13,14] Additional information on household with a broadband internet subscription was abstracted from the SVI dataset.

Statistical analysis

Descriptive statistics were calculated using frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. Differences in county-level characteristics were calculated using measures of effect size such as Cohen's d (i.e., the standardized mean difference; small: 0.2, medium: 0.5, large: 0.8) or Cramer's V—which is based on the chi-square statistic. V of 0.1 is considered a small effect, 0.3 a medium effect, and 0.5 a large effect when comparing across two categories; 0.1 a small effect, 0.25 a medium effect, and 0.4 a large effect when comparing across more than two categories.[15] Risk ratios (RR) and 95% confidence intervals (CI) were estimated using modified Poisson regression models with robust standard errors evaluating the association between county-level demographics and availability of an NCORP or NCI site. Because the data contain information on almost all US counties (i.e., there is no sampling of counties), inferential quantities measuring sampling uncertainty such as standard errors and CIs are applicable to different periods of time (i.e., the current time-period constitutes one random period taken from the population of cohort time periods). The first set of models assessed singular county access to sites while the second

set assessed county and its contiguous counties access to sites. For the first set of models (singular county), the following predictor variables were included for NCORP & NCI availability: 1) SVI overall theme continuous; 2) SVI overall theme dichotomized. For NCORP site availability, a third model was fitted containing, as predictors, all four SVI themes and RUCC. However, zero singular rural counties had an NCI site therefore, the singular county third model for NCI availability was fitted containing only the four SVI themes. For the second set of models (contiguous), the following predictors were included for both NCORP and NCI site availability: 1) SVI overall theme continuous; 2) SVI overall theme dichotomized; 3) all four themes and RUCC. Analyses were performed and maps were created using and SAS© software, version 9.4 (SAS Institute, Cary, NC). Geocoding was performed using Esri ArcGIS Pro software, version 2.5.0.

Results

County-level characteristics

Of the 3143 US counties, we were able to include 3141 counties in our analysis. Two counties were excluded due to missing information on rurality[16] (Supplemental Table 1). Only 448 (14%) of counties contained at least one NCORP site and 53 counties had at least one NCI site (2%; Table 1). Of the counties containing an NCORP site, 44% were in the Midwestern region and 71% were in metropolitan counties. All but one county with an NCI site were metropolitan. Furthermore, 32 metropolitan counties in the US had both an NCORP and an NCI site (Figure 1). In all regions of the US, NCORP sites appeared to be clustered in counties not considered the most vulnerable (Figure 2).

Descriptive differences in counties by availability of NCORP & NCI sites

When assessing variables that make up each theme, on average, counties with an NCORP site had fewer individuals who lived in poverty (mean percentage: 21 vs 25), fewer individuals without a high school diploma (10 vs 13), fewer individuals were 65 year and older (17 vs 20) more multi-unit structures (10 vs 4), and fewer people without internet (12 vs 18) when compared to counties without NCORP nor NCI sites. Counties with NCI sites were more racially diverse (50 vs 24), and more individuals lived in multi-unit structures (22 vs 4). Counties with both sites were the most vulnerable with the overall theme mean score 0.70 (SD 0.18) compared to those without sites (0.50 SD 0.29), counties with an NCORP site (0.51 SD 0.27), or counties with an NCI site (0.67 0.21). When we assessed the county and its contiguous counties as having an NCORP (n=1409, 45% of all counties) or NCI site (n=263, 8%), both areas were less vulnerable when compared to counties without NCORP nor NCI sites (Table 2). The contiguous counties with NCORP access were more suburban (contiguous 30% vs singular 22%) while contiguous counties with NCI access had less racial and ethnic marginalized groups (contiguous 31% vs singular 50%).

Model results of singular counties

In our first set of models which assessed singular counties containing at least one NCORP site versus all other counties, we found the counties with the highest vulnerability (according to the overall SVI theme) had 31% lower probability of containing an NCORP site when compared to the other 90% of counties (95% CI 0.49-0.97; Table 3). However, NCI sites were located in more vulnerable counties overall;

compared to the other 90% of counties, the most vulnerable counties had 1.59 times the probability of NCI sites being available (95% CI 0.76-3.35). When assessing the model with all four themes and RUCC for NCORP availability, we found each variable to be significant. With a one-SD increase of the socioeconomic theme score (or as counties become more vulnerable), there was a 24% lower probability of an NCORP site being available (RR 0.76, 95% CI 0.67-0.87) and with a one-SD increase of the household characteristics theme there was a 11% lower probability (95% CI 0.80-0.99). However, for both the racial and ethnic minority status theme and housing type & transportation theme, there was a 1.22 (95% CI 1.10-1.36) and 1.33 (95% CI 1.20-1.47) times higher probability of NCORP availability, respectively. Furthermore, compared to rural areas, both metropolitan and suburban areas had higher probability of an available NCORP site. Results were similar for the model assessing NCI availability. However the magnitude of the effects were larger, for example, with one-SD increase of the racial and ethnic minority status theme, there was six times the probability of NCI availability (95% CI 4.09-8.81).

Model results of contiguous counties

In the models which assessed the probability of counties & their corresponding contiguous counties having at least one site, NCORP results were similar to the singular county models except when the counties and the contiguous counties become more racially and ethnically diverse, there was no difference in availability of NCORP sites (RR 1.03, 95% CI 0.98-1.08; Table 4). For models assessing availability of an NCI site in counties & contiguous counties, SVI overall theme results were similar to the NCORP

model results: when vulnerability increased there was a lower probability of having NCI site availability (overall theme continuous RR 0.83, 95% CI 0.75-0.94), which differs from our singular county NCI model. Furthermore, for the model containing all four themes and RUCC, results for NCI availability were similar to the singular model expect for the racial & ethnic minority status theme. As these areas become more racially diverse, there is a 1.97 times the probability of an available NCI site (95% CI 1.68-2.32). For both the NCORP and NCI models, metropolitan and suburban areas had higher probabilities of having NCORP or NCI sites when compared to rural areas.

Discussion

We found that the majority of counties do not have access to NCORP, a federally-funded program that is designed to bring cancer clinical trials to the community. While we found that singular counties with higher proportions with marginalized racial and ethnic groups had higher probabilities of having access to NCORP sites, this is likely explained by NCORP's Minority/Underserved Community Sites. These sites appear to be appropriately located in singular counties that serve racially and ethnically diverse populations. However, for continuous counties as marginalized racial groups increased there was a similar probability of availability of NCORP sites, while conversely, there was a higher probability of NCI site availability. Previous studies have assessed availability of specific clinical trials within specific cancer types at the county level; however, our study evaluated access to sites that have the resources (i.e., financial, staffing, medical equipment) to conduct a clinical trial via their NCORP or NCI status within singular and contiguous county. Wang et al found that US counties with higher

proportions of African Americans are less likely to have access to any prostate cancer clinical trials.[17] Additionally, Grant et al assessed the association between SVI themes and availability of multiple myeloma trials within North Carolina and found similar results to Wang et al.[18] While these studies assessed clinical trial availability differently than ours, the need for more NCORP community sites to serve a wider catchment area of marginalized racial groups who are underrepresented in clinical trials is evident throughout. Additionally, increasing accessibility is a necessary piece in overcoming underrepresentation for this particular patient population, especially as NCORP sites have reported that the population they serve is 79% White.[7]

Another interesting finding is that all NCI sites were located in metropolitan counties and metropolitan and suburban vs rural counties had higher probabilities of having availability of NCORP sites; therefore, NCORP sites are reaching individuals in metropolitan areas. However, patients outside of metropolitan areas may have distinct risks and health care needs. Research has shown that the health of the community and the built environment is influential on individual-level health.[19-22] [23] Zhang et al found that there is a strong relationship between the proximity to landfills and a diagnosis of bladder, breast, and liver cancer. [24] Furthermore, they found the proximity to major roads and industry was associated with a diagnosis of lung cancer. Particularly, the urbanicity of a community can drive greater access to healthcare as often urban areas have more public transportation whereas rural areas face distance barriers.[25-27]

Compounded with rurality, the socioeconomic status (SES) of the community is important, as these higher levels of SES has been shown to be associated with more access to healthcare[28,29] and clinical trial enrollment.[30] We found that as contiguous

counties become more socioeconomically vulnerable, there was 8% and 41% lower probability of availability of NCORP and NCI sites, respectively. One's SES status is associated with not only place, race, insurance status, but also education, income, and employment, which affect cancer outcomes.[31] For example, individuals living in rural or lower SES locations often present to clinic in more advanced cancer stages which is associated with poorer survival and they more often receive delayed cancer care.[32-34] These results point to the issue so many programs face, that we are not reaching the truly vulnerable places. Even though community sites are closing or being acquired by other hospitals[35], there is a need to include additional sites that are still open in rural or poorer locations into the NCORP network. In 2018, Carlos et al assessed the 2018 Landscape Capacity Assessment survey conducted at 46 NCORP Community Sites and found that NCORP sites include independent community practices, health system-affiliated practices, and safety-net hospitals.[36] Therefore, the idea of working with academic medical centers who either open new or conglomerate with existing locations within these areas appears to be feasible. It is imperative for health care systems to change to bring clinical trial availability and health care access to more patients.

Additionally, the inclusion of the individuals without broadband internet is of great importance for the future of medical care services, including clinical trials. Since the COVID-19 pandemic, there has been an increase in the use of telemedicine; furthermore, clinical trials are shifting their practice to include more use of telemedicine in hopes of alleviating transportation barriers and increasing participation.[37-39] The Pew Research Center has found that those with increasing education and income more often have in-home internet.[40] While individuals in counties with these sites more often have

internet then counties without, this should be a consideration when expanding NCORP sites. If clinical trials are to increase the use of telemedicine, sites will want to mitigate inequities surrounding internet access, especially as those who do not have internet may already be likely to be underrepresented and, thus, more likely to have poorer outcomes (e.g., disability, disease, death).[41] Future research is needed to understand the intersectionality of transportation obstacles, financial barriers and internet access, especially as it relates to health care seeking behaviors and clinical trial participation.

This study should be considered in light of several limitations. As this is an exploratory analysis, we were unable to ascertain a causal link between county-level data and inclusion of NCORP or NCI sites. Consideration of when sites were included in NCORP or were designated NCI Cancer Centers, which is outside of the scope of this research. Also, we were unable to determine how the counties with access multiple NCORP and/or NCI sites differ from counties with one site and if there is a "dose" effect. Additionally, by using exploratory associations at the county level, there is potential that ecological fallacies are present. Finally, these findings are meant to be interpreted at the county level and therefore may not represent individual-level data and experiences.

Conclusion

NCORP and NCI sites serve as proxies for access to clinical trials. Unfortunately, NCORP sites are largely not in counties nor do they serve contiguous counties with populations underrepresented in clinical trials; whereas NCI sites are located in areas that serve marginalized racial and ethnic groups. There are fewer NCI sites than NCORP sites, therefore, the reach of NCORP is much greater as is the need, especially in poorer

areas, as these individuals face the greatest disease burden. More research is needed to understand how patient representation in clinical trials will increase if NCORP sites partner with more community oncology and academic satellite sites in a strategic way.

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Figure legend

Figure 1. Map of the US counties by Rural Urban Continuum Codes (metropolitan, suburban, rural) with red dots representing counties containing National Cancer Institute National Cancer Oncology Research Program sites, black dots representing counties containing National Cancer Institute sites, and yellow dots representing counties with both.

Figure 2. Map of the US counties by Social Vulnerability Index's overall vulnerability theme of high vulnerable counties (upper 10%) and 90% of other counties with red dots representing counties containing National Cancer Institute National Cancer Oncology Research Program sites, black dots representing counties containing National Cancer Institute sites, and yellow dots representing counties with both.

Table 1. County-level Social Vulnerability Index demographics of total counties (N=3141), counties without an NCORP nor NCI sites (n=2672), counties containing an NCORP site (n=448), counties containing an NCI site (n=53), and counties containing both NCORP and NCI sites (n=32).

	Total N=3141	**Counties without an NCORP nor NCI site** n=2672	**Counties containing an NCORP site** n=448	**Counties containing an NCI site** n=53	**Counties containing both NCORP and NCI sites** n=32
	n (%) or mean (SD)				
Region					
Midwest	1055 (33.6)	853 (31.9)	197 (44.0)	13 (24.5)	8 (25.0)
Northeast	217 (6.9)	175 (6.6)	36 (8.0)	9 (17.0)	3 (9.4)
South	1422 (45.3)	1288 (48.2)	126 (28.1)	18 (34.0)	10 (31.2)
West	447 (14.2)	356 (13.3)	89 (19.9)	13 (24.5)	11 (34.4)
Rural-Urban Continuum Codes					
1-3: Metropolitan	1166 (37.1)	828 (31.0)	318 (71.0)	52 (98.1)	32 (100)
4-6: Suburban	899 (28.6)	799 (29.9)	99 (22.1)	1 (1.9)	
7-9: Rural	1076 (34.3)	1045 (39.1)	31 (6.9)		
Overall theme, mean (SD)	0.50 (0.29)	0.50 (0.29)	0.51 (0.27)	0.67 (0.21)	0.70 (0.18)
Overall theme dichotomized					
High vulnerable (upper 10%)	315 (10.0)	279 (10.4)	32 (7.1)	8 (15.1)	4 (12.5)
90% other counties	2826 (90.0)	2393 (89.6)	416 (92.9)	45 (84.9)	28 (87.5)
Socioeconomic status theme, mean (SD)	0.50 (0.29)	0.50 (0.29)	0.49 (0.27)	0.61 (0.26)	0.63 (0.24)
Percentage of persons below 150% poverty, mean (SD)	24.5 (8.5)	25.0 (8.6)	21.3 (7.0)	22.6 (5.8)	22.3 (6.2)
Unemployment rate estimate,	5.2 (2.6)	5.2 (2.7)	5.1 (1.6)	5.4 (1.5)	5.6 (1.4)

mean (SD)					
Percentage of housing cost burden, mean (SD)	22.3 (5.3)	21.7 (5.1)	25.5 (4.9)	30.3 (4.9)	30.7 (5.5)
Percentage of person with no high school diploma, mean (SD)	12.4 (6.0)	12.8 (6.2)	9.9 (4.3)	11.1 (4.5)	11.8 (4.6)
Percentage uninsured, mean (SD)	9.5 (5.1)	9.8 (5.3)	7.7 (3.4)	8.4 (4.3)	8.5 (3.9)
Household characteristics theme, mean (SD)	0.50 (0.29)	0.51 (0.29)	0.45 (0.27)	0.42 (0.29)	0.42 (0.29)
Percentage of persons aged 65 & older, mean (SD)	19.2 (4.8)	19.6 (4.8)	17.4 (4.1)	14.3 (2.3)	14.1 (1.6)
Percentage of persons aged 17 & younger, mean (SD)	22.1 (3.6)	22.1 (3.7)	22.1 (2.7)	21.4 (3.2)	21.6 (3.2)
Percentage of civilians with a disability, mean (SD)	16.0 (4.5)	16.4 (4.5)	13.7 (3.5)	11.7 (2.4)	11.6 (2.1)
Percentage of single-parent households, mean (SD)	5.9 (2.4)	5.8 (2.5)	6.2 (1.8)	6.8 (1.9)	6.8 (2.1)
Percentage of individuals who speak English “less than well”, mean (SD)	1.6 (2.7)	1.5 (2.7)	2.1 (2.7)	5.1 (4.0)	5.9 (4.31)
Racial & ethnic minority status theme, mean (SD)	0.50 (0.29)	0.48 (0.29)	0.57(0.26)	0.83 (0.14)	0.87 (0.10)
Percentage of individuals who are of racial & ethnic	24.2 (20.2)	23.5 (20.2)	28.1 (19.9)	49.8 (18.5)	55.0 (16.5)

marginalized groups, mean (SD)					
Housing type & transportation theme, mean (SD)	0.50 (0.29)	0.49 (0.29)	0.57 (0.27)	0.78 (0.13)	0.80 (0.12)
Percentage of multi-unit structures, mean (SD)	4.8 (5.8)	3.8 (4.6)	9.9 (8.5)	22.2 (13.9)	24.9 (16.7)
Percentage of mobile homes, mean (SD)	12.6 (9.5)	13.7 (9.6)	6.6 (6.2)	2.2 (2.2)	2.0 (1.9)
Percentage of overcrowded housing, mean (SD)	2.4 (2.4)	2.4 (2.5)	2.4 (1.9)	3.7 (2.6)	4.5 (2.9)
Percentage of household with no vehicles, mean (SD)	6.2 (4.5)	6.0 (4.2)	6.9 (5.9)	13.0 (13.4)	14.1 (16.0)
Percentage of individuals in group quarters, mean (SD)	3.5 (4.5)	3.6 (4.8)	2.8 (2.2)	2.9 (1.7)	2.5 (1.2)
Percentage without computer with broadband internet, mean (SD)	16.9 (7.6)	17.7 (7.7)	12.3 (5.1)	12.3 (5.1)	10.8 (3.9)

NCORP=National Cancer Institute Community Oncology Research Program;

NCI=National Cancer Institute; SD=standard deviation.

Table 2. County-level Social Vulnerability Index demographics of the counties containing a NCORP site and the contiguous counties (n=1409) and counties containing an NCI site and their contiguous counties (n=263).

	Contiguous counties with an NCORP site n=1409	**Contiguous counties with an NCI site n=263**
	n (%) or mean (SD)	
Region		
Midwest	585 (41.5)	74 (28.1)
Northeast	83 (5.9)	43 (16.4)
South	490 (34.8)	86 (32.7)
West	251 (17.8)	60 (22.8)
Rural-Urban Continuum Codes		
1-3: Metropolitan	682 (48.4)	216 (82.1)
4-6: Suburban	417 (29.6)	37 (14.1)
7-9: Rural	310 (22.0)	10 (3.8)
Overall theme, mean (SD)	0.47 (0.29)	0.45 (0.28)
Overall theme dichotomized		
High vulnerable (upper 10%)	107 (7.6)	15 (5.7)
90% other counties	1302 (92.4)	248 (94.3)
Socioeconomic status theme, mean (SD)	0.47 (0.29)	0.43 (0.27)
Percentage of persons below 150% poverty, mean (SD)	22.8 (7.8)	18.0 (6.5)
Unemployment rate estimate, mean (SD)	5.2 (2.1)	4.9 (1.6730145)
Percentage of housing cost burden, mean (SD)	23.0 (5.0)	24.3 (5.1)
Percentage of person with no high school diploma, mean (SD)	11.3 (5.3)	10.1 (4.9)
Percentage uninsured, mean (SD)	8.4 (4.1)	7.4 (3.6)
Household characteristics theme, mean (SD)	0.47 (0.28)	0.43 (0.26)
Percentage of persons aged 65 & older, mean (SD)	19.0 (4.6)	16.5 (3.7)
Percentage of persons aged 17 & younger, mean (SD)	21.8 (3.2)	22.7 (3.1)
Percentage of civilians with a disability, mean (SD)	15.2 (4.0)	12.4 (3.2)
Percentage of single-parent households, mean (SD)	5.8 (2.1)	6.0 (1.6)

Percentage of individuals who speak English “less than well”, mean (SD)	1.6 (2.5)	3.0 (3.3)
Racial & ethnic minority status theme, mean (SD)	0.50 (0.28)	0.61 (0.26)
Percentage of individuals who are of racial & ethnic marginalized groups, mean (SD)	23.6 (19.2)	31.0 (21.0)
Housing type & transportation theme, mean (SD)	0.48 (0.29)	0.47 (0.28)
Percentage of multi-unit structures, mean (SD)	5.6 (6.6)	9.89 (10.2)
Percentage of mobile homes, mean (SD)	11.34 (9.5)	7.1 (7.9)
Percentage of overcrowded housing, mean (SD)	2.3 (1.8)	2.8 (2.3)
Percentage of household with no vehicles, mean (SD)	5.9 (4.2)	6.0 (7.1)
Percentage of individuals in group quarters, mean (SD)	3.2 (3.9)	2.3 (1.9)
Percentage without computer with broadband internet, mean (SD)	15.3 (6.9)	10.7 (4.8)

NCORP=National Cancer Institute Community Oncology Research Program;

NCI=National Cancer Institute; SD=standard deviation.

Table 3. Model-estimated risks ratios, 95% confidence intervals, and predicted proportions evaluating the association between county-level demographics and availability of NCORP and NCI sites in singular counties (N=3141).

Availability of NCORP sites	**Risk ratios (95% CI)**	**Predicted proportions**
Model 1 (N=3141), reference proportion 0.14		
Overall theme continuous, SD increase	1.05 (0.97-1.14)	0.15
Model 2 (N=3141)		
Overall theme dichotomized		
Upper 10%, high vulnerable	**0.69 (0.49-0.97)**	0.10
Other 90% of counties	Reference	0.15
Model 3 (N=3141), reference proportion 0.09		
Socioeconomic status theme, SD increase	**0.76 (0.67-0.87)**	0.07
Household characteristics theme, SD increase	**0.89 (0.80-0.99)**	0.08
Racial & ethnic minority status theme, SD increase	**1.22 (1.10-1.36)**	0.11
Housing type & transportation theme, SD increase	**1.33 (1.20-1.47)**	0.12
Rural-Urban Continuum Codes		
Metropolitan	**8.35 (5.85-11.91)**	0.24
Suburban	**3.76 (2.52-5.61)**	0.11
Rural	Reference	0.03
Availability of NCI sites	**Risk ratios (95% CI)**	**Predicted proportions**
Model 1 (N=3141), reference proportion 0.01		
Overall theme continuous, SD increase	**1.91 (1.50-2.45)**	0.03
Model 2 (N=3141)		
Overall theme dichotomized		
Upper 10%, high vulnerable	1.59 (0.76-3.35)	0.03
Other 90% of counties	Reference	0.02
Models 3 (N=3141), reference proportion 0.004		
Socioeconomic status theme, SD increase	**0.71 (0.53-0.96)**	0.003
Household characteristics theme, SD increase	**0.51 (0.40-0.65)**	0.002
Racial & ethnic minority status theme, SD increase	**6.00 (4.09-8.81)**	0.02
Housing type & transportation theme, SD increase	**2.04 (1.58-2.63)**	0.007

Models 1 and 2 only contain the Social Vulnerability Index (SVI) overall theme; model 3 contains all four SVI themes (NCI only) and Rural Urban Continuum Codes. Bolded values represented significance at the 0.05 alpha level. NCORP= National Cancer Institute Community Oncology Research Program; NCI=National Cancer Institute; CI=confidence intervals.

Table 4. Model-estimated risks ratios, 95% confidence intervals, and predicted proportions evaluating the association between county-level demographics and availability of NCORP and NCI sites in contiguous counties (N=3141).

Availability of NCORP sites	**Risk ratios (95% CI)**	**Predicted proportions**
Model 1 (N=3141), reference proportion 0.45		
Overall theme continuous, SD increase	**0.91 (0.87-0.94)**	0.41
Model 2 (N=3141)		
Overall theme dichotomized		
Upper 10%, high vulnerable	**0.74 (0.63-0.86)**	0.34
Other 90% of counties	Reference	0.46
Model 3 (N=3141), reference proportion 0.43		
Socioeconomic status theme, SD increase	**0.92 (0.86-0.98)**	0.39
Household characteristics theme, SD increase	0.95 (0.90-1.00)	0.40
Racial & ethnic minority status theme, SD increase	1.03 (0.98-1.08)	0.44
Housing type & transportation theme, SD increase	0.96 (0.92-1.01)	0.41
Rural-Urban Continuum Codes		
Metropolitan	**2.03 (1.82-2.26)**	0.57
Suburban	**1.72 (1.53-1.93)**	0.48
Rural	Reference	0.28
Availability of NCI sites	**Risk ratios (95% CI)**	**Predicted proportions**
Model 1 (N=3141), reference proportion 0.08		
Overall theme continuous, SD increase	**0.83 (0.75-0.94)**	0.07
Model 2 (N=3141)		
Overall theme dichotomized		
Upper 10%, high vulnerable	**0.54 (0.33-0.90)**	0.05
Other 90% of counties	Reference	0.09
Model 3 (N=3141), reference proportion 0.04		
Socioeconomic status theme, SD increase	**0.59 (0.49-0.72)**	0.02
Household characteristics theme, SD increase	0.92 (0.79-1.06)	0.03
Racial & ethnic minority status theme, SD increase	**1.97 (1.68-2.32)**	0.07
Housing type & transportation theme, SD increase	0.89 (0.78-1.01)	0.03
Rural-Urban Continuum Codes		
Metropolitan	**16.20 (8.64-30.39)**	0.13
Suburban	**5.41 (2.68-10.91)**	0.04
Rural	Reference	0.01

Models 1 and 2 only contain the Social Vulnerability Index (SVI) overall theme; model 3 contains all SVI four themes and Rural-Urban Continuum Codes. Bolded values

represented significance at the 0.05 alpha level. NCORP= National Cancer Institute Community Oncology Research Program; NCI=National Cancer Institute; CI=confidence intervals.

Figure 1. Map of the US counties by Rural Urban Continuum Codes (metropolitan, suburban, rural) with red dots representing counties containing National Cancer Institute National Cancer Oncology Research Program sites, black dots representing counties containing National Cancer Institute sites, and yellow dots representing counties with both.

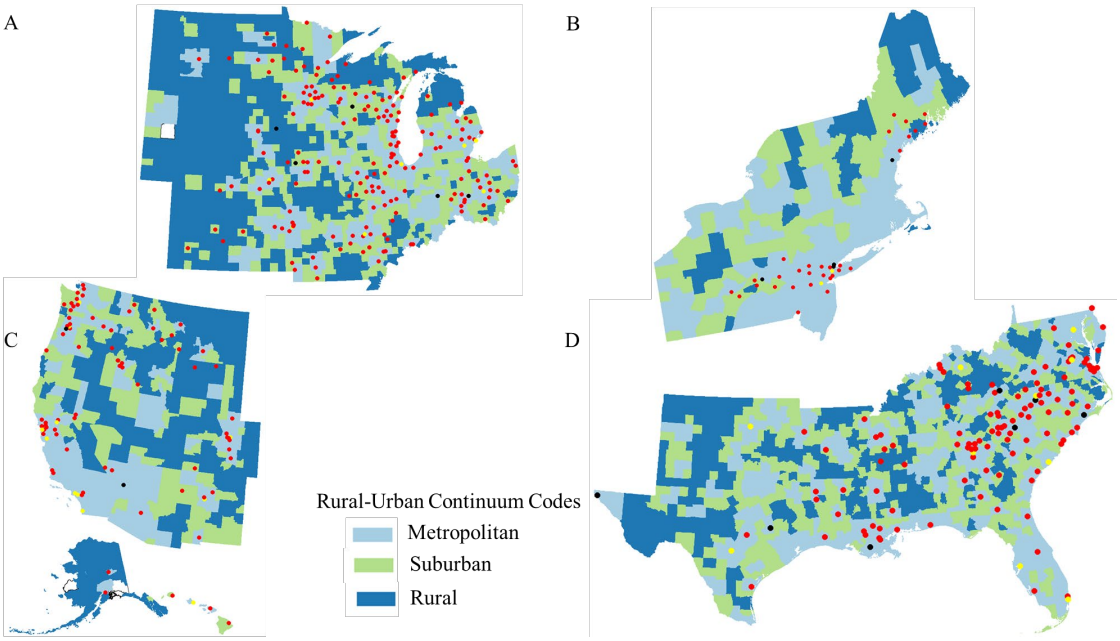
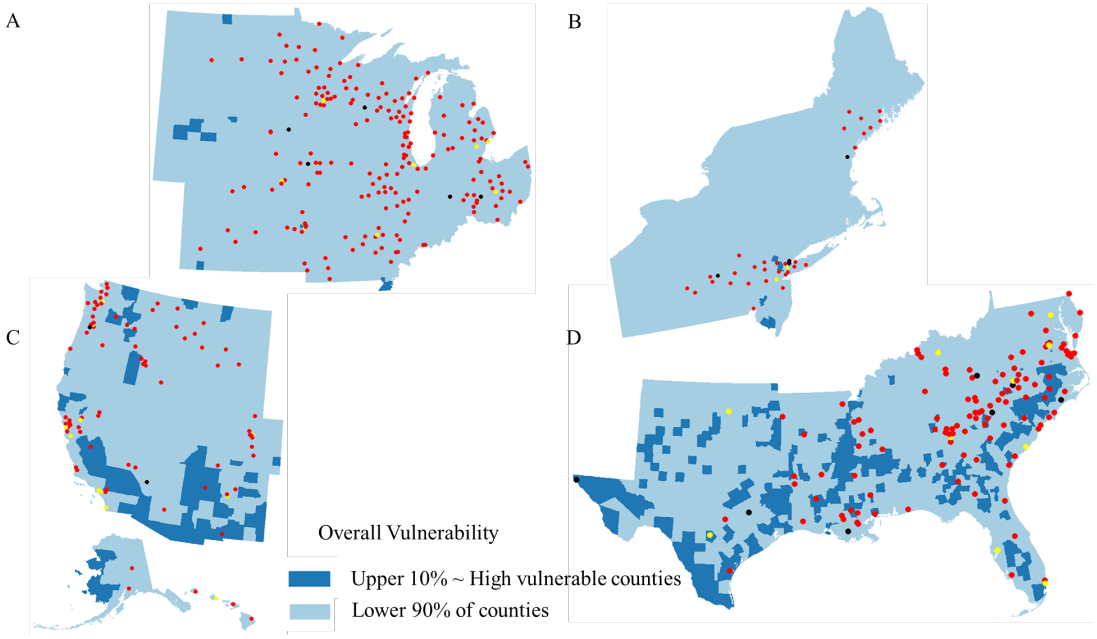


Figure 2. Map of the US counties by Social Vulnerability Index's overall vulnerability theme of high vulnerable counties (upper 10%) and 90% of other counties with red dots representing counties containing National Cancer Institute National Cancer Oncology Research Program sites, black dots representing counties containing National Cancer Institute sites, and yellow dots representing counties with both.



Supplemental Table 1. County-level Social Vulnerability Index demographics of counties included in the analysis (n=3141) and excluded (n=2).

	Included in the analysis N=3141	**Excluded from the analysis n=2**	**Cramer's V or Cohen's d**
Region			0.06
Midwest	1055 (33.6)		
Northeast	217 (6.9)		
South	1422 (45.3)		
West	447 (14.2)	2 (100)	
Rural-Urban Continuum Codes			NA
1-3: Metropolitan	1166 (37.1)		
4-6: Suburban	899 (28.6)		
7-9: Rural	1076 (34.3)		
Overall theme, mean (SD)	0.50 (0.29)	0.31 (0.11)	0.67
Overall theme dichotomized			0.01
High vulnerable (upper 10%)	315 (10.0)		
90% other counties	2826 (90.0)	2 (100)	
Socioeconomic status theme, mean (SD)	0.50 (0.29)	0.20 (0.16)	1.04
Percentage of persons below 150% poverty, mean (SD)	24.5 (8.5)	13.4 (9.3)	1.30
Unemployment rate estimate, mean (SD)	5.2 (2.6)	4.2 (2.0)	0.39
Percentage of housing cost burden, mean (SD)	22.3 (5.3)	17.0 (0.6)	1.00
Percentage of person with no high school diploma, mean (SD)	12.4 (6.0)	4.5 (0.1)	1.31
Percentage uninsured, mean (SD)	9.5 (5.1)	17.4 (3.5)	1.54
Household characteristics theme, mean (SD)	0.50 (0.29)	0.18 (0.23)	1.12
Percentage of persons aged 65 & older, mean (SD)	19.2 (4.8)	12.9 (0.8)	1.33
Percentage of persons aged 17 & younger, mean (SD)	22.1 (3.6)	24.6 (4.5)	0.70
Percentage of civilians with a disability, mean (SD)	16.0 (4.5)	13.8 (3.6)	0.50
Percentage of single-parent households, mean (SD)	5.9 (2.4)	4.8 (2.6)	0.47

Percentage of individuals who speak English “less than well”, mean (SD)	1.6 (2.7)	0.3 (0.4)	0.49
Racial & ethnic minority status theme, mean (SD)	0.50 (0.29)	0.73 (0.13)	0.81
Percentage of individuals who are of racial & ethnic marginalized groups, mean (SD)	24.2 (20.2)	35.0 (11.7)	0.53
Housing type & transportation theme, mean (SD)	0.50 (0.29)	0.65 (0.39)	0.52
Percentage of multi-unit structures, mean (SD)	4.8 (5.8)	4.0 (4.2)	0.14
Percentage of mobile homes, mean (SD)	12.6 (9.5)	12.1 (7.4)	0.06
Percentage of overcrowded housing, mean (SD)	2.4 (2.4)	4.6 (0.4)	0.92
Percentage of household with no vehicles, mean (SD)	6.2 (4.5)	5.9 (2.3)	0.07
Percentage of individuals in group quarters, mean (SD)	3.5 (4.5)	2.2 (1.9)	0.30
Percentage without computer that has broadband internet, mean (SD)	16.9 (7.6)	14.7 (5.3)	0.30

NCORP= National Cancer Institute Community Oncology Research Program;

NCI=National Cancer Institute; SD=standard deviation.

WILL PATIENTS BE MORE WILLING TO PARTICIPATE IN CANCER CLINICAL TRIALS IF SYSTEM-LEVEL CHANGES ARE MADE?

by

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Abstract

Introduction: Over the course of the COVID-19 pandemic, the Food and Drug Administration allowed for patient-centric modifications to be made to cancer clinical trials. While these changes may be beneficial, patient perspectives must be ascertained as to neither create nor exacerbate disparities.

Methods: This cross-sectional study used survey data fielded in 12/2022 from individuals with breast cancer who had previously received services from the Patient Advocate Foundation. Reported willingness to participate in a clinical trial based on trial system changes in location, telemedicine availability, convenience, and opting out was assessed for association with respondent's neighborhood-level area deprivation and prior clinical trial participation. Risk ratios (RR) and 95% confidence intervals were estimated using modified Poisson regression models.

Results: A total of 285 women were included. Overall, 14% lived in higher disadvantaged areas and 14% had previously participated in a trial. The trial modification viewed most favorably was medications being delivered to the home with 49% reporting they would be very willing to participate based on this change. When compared to individuals who had previously participated, those who had never participated in a trial had higher probabilities (RR range 1.20-2.08) of being willing to participate given each systems-level change. Furthermore, individuals in higher vs lower disadvantaged areas had similar probabilities of being willing to participate.

Conclusion: Overall, our sample of socioeconomically vulnerable individuals viewed these trial modifications favorably, specifically respondents who had never participated. Furthermore, these changes have the potential to increase clinical trial participation.

Background

During the course of the COVID-19 pandemic, healthcare access, delivery, and utilization changed.[1] To alleviate issues surrounding the inability for sponsors to successfully carry out clinical trial procedures, the Food and Drug Administration (FDA) allowed for more flexible adaptations, including telemedicine, location changes, and schedule flexibility and convenience.[2-6] The modifications made to several treatment trials were beneficial; trials that made these changes had only a small reduction in enrollment despite the COVID-19 pandemic.[3] Therefore, the FDA Oncology Center of Excellence has called for increased efforts to decentralize clinical trials.[6] Another important area of transformation to the healthcare system was the rise of telecommunicating.[7] For example, prior to the pandemic, only less than 1% of claims were telehealth, while during the pandemic it was as high as 13%.[8] Following the peak of the pandemic; telehealth has continued; in January 2023, 5.9% of claims were attributed to telehealth while it was 5.5% in December 2022.[7] With the continued use of telecommunication and the ability for trial to adapt, it is likely that future trials will also offer flexible options.

Patient-centric changes that occurred during the pandemic may be uniquely beneficial to patients known to be underrepresented in clinical trials. However, before the widespread implementation of these changes, the scientific community needs to ask patients their perspectives on these trial changes, especially for underrepresented patient populations. For example, patients who reside in areas of higher disadvantage (per Area Deprivation Index) already face lower incomes and educational levels.[9] Additionally, patients living in disadvantaged or rural areas more often face transportation barriers;[10]

therefore, telemedicine has the potential to increase participation of those who are geographically distant to clinical trial sites. At the same time, these changes to clinical trials could exacerbate known disparities. In 2021, according to the Pew Research Center, 57% of those with less than $30K in income had in-home internet whereas 74% of those making between $30K and $50K had in-home internet access. Similar results were seen across education levels.[11]

Understanding if these changes would influence trial participation for individuals living in areas of higher disadvantage is important to overcoming underrepresentation of this patient population and ensuring disparities are not created or exacerbated. To mitigate current or future disparities, the objective of our study is to understand patients' willingness to participate in future breast cancer clinical trials based on cancer clinical trial changes by their area's disadvantage.

Methods

Study design and participants

This cross-sectional study used survey data from a nationwide cohort of female breast cancer survivors. This survey (Supplemental Figure) was fielded from 12/06/2022 through 12/31/2022 by Patient Advocate Foundation (PAF) to individuals who were recently served by PAF. PAF is a nonprofit organization that provides social needs navigation and financial aid to patients diagnosed with a chronic illness. Patients seeking services from PAF face healthcare access and affordability challenges. Many of these patients represent marginalized populations, face a variety of social needs, and are limited in the resources they have available to meet both medical and non-medical needs.[12] This

study included women with a diagnosis of breast cancer at any stage within the last five years or metastatic breast cancer at any time. Additional inclusion criteria included the ability to complete the survey in English, aged > 18 years of age, and being a US resident. All survey questions were required which ensured complete data capture. In order to have a more robust sample of individuals who are typically underrepresented in clinical trials, we sent more reminders to individuals living in higher disadvantaged areas and who are Black, Indigenous, or a Person of Color (BIPOC). This study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB-300010015).

Outcomes

Willingness to participate in cancer clinical trials: A total of 11 questions were asked regarding willingness to participate in clinical trials based on three major types of changes to trials (Supplemental Figure). These categories included location changes for certain procedures (blood tests, X-ray tests, doctor visits with doctor not involved in trial), use of secure telemedicine portal (for trial doctor visits, online consent form, online questionnaires), and trial flexibility and convenience, which was broken into convenience (fewer trial site visits, delivery of medications to the home, increased flexibility in completing visits, treatment, procedures) and opting out of procedures (opt out of blood test that do not affect care, opt out of biopsies that do not affect care). Each question was measured on a Likert scale with the following: 1) much less likely to participate; 2) somewhat less likely to participate; 3) would not affect my decision whether or not to participate; 4) somewhat more likely to participate; 5) much more likely to participate.

For our models, we grouped respondents as being willing (scores 4 and 5) versus those who are or unwilling or no change (scores 1, 2, 3).

Exposures

Neighborhood-level area deprivation: Survey respondents were grouped into either living in areas of higher disadvantage or lower disadvantage according to Area Deprivation Index (ADI) scores. ADI determines the neighborhood disadvantage based on census block group education, income, employment, and housing quality.[9] Patient addresses were mapped to 12-digit Federal Information Processing Standard codes and grouped into area disadvantage by PAF prior to data transfer. ADI scores range from 1-100%, with scores 86-100 representing higher disadvantaged areas and 1-85 representing lower disadvantaged areas. This dichotomization of ADI levels is in accordance with ADI creators Kind and colleagues.[13]

Breast cancer clinical trial participation: Respondents were asked if they had ever participated in a clinical trial; response options were yes or no.

Patient demographics and clinical characteristics

Patient age at diagnosis (49 or younger, 50 or older), race (American Indian/Alaska Native, Asian, Black or African American, more than one race, Native Hawaiian or Other Pacific Islander, other, White/Caucasian), ethnicity (Hispanic or Latino(a) or non-Hispanic or Latino(a) origin or descent), education level (high school or less, some college, Bachelor's degree or greater), annual household income ($49,000 or less, $50,000 or more), employment status (disabled, employed, retired, unemployed/other),

cancer stage (early [with or without lymph node involvement], late [having spread to other parts of the body]), and time since diagnosis (less than five years, 5-10 years, more than ten years ago) were self-reported by survey respondents. Additionally, individuals reported if a breast cancer provider had ever discussed a breast cancer clinical trial with them (yes, no). Respondents also reported their typical travel time to appointments with the breast cancer provider they see the most regularly (less than 30 minutes, 30-60 minutes, 1 hour or greater). Baseline willingness to participate in a clinical trial was assessed by asking respondents their willingness to participate in a trial if they had not participated in a trial. This question was measured on a five-point Likert scale with the following: 1) not willing at all; 2) not really willing; 3) undecided; 4) somewhat willing; 5) very willing. Participants who had ever participated were categorized as having a "very willing" baseline willingness to participate.

Statistical analysis

Descriptive statistics were calculated using frequencies and percentages for categorical variables; means and standard deviations or medians and interquartile ranges for continuous variables. Differences in characteristics for respondents living in higher or lower disadvantaged areas were calculated using measures of effect size such as Cohen's d (i.e., the standardized mean difference; small: 0.2, medium: 0.5, large: 0.8) for numerical characteristics or Cramer's V for cross-tabulations. V of 0.1 is considered a small effect, 0.3 a medium effect, and 0.5 a large effect when comparing across two categories; 0.1 a small effect, 0.25 a medium effect, and 0.4 a large effect when comparing across more than two categories.[14] We conducted dimension reduction in the

form of a principal components analysis (PCA) to determine empirically whether survey questions could be averaged across overarching type of clinical trial change (when the proportion of the total variance for the first eigenvalue was greater than or equal to 0.70). Using four modified Poisson regression models with robust standard errors, we estimated risk ratios (RR), predicted probabilities, and 95% confidence intervals (CI) to evaluate the association between participation and area deprivation on willingness to participate in a breast cancer clinical trial due to 1) location changes; 2) telemedicine use; 3) convenience of trial; and 4) opting out of trial procedures. Models were adjusted for age at diagnosis, race (due to small numbers, categories with less than 20 individuals were grouped into a singular group for modeling purposes), ethnicity, cancer stage, travel time to cancer center, and baseline willingness to participate in a clinical trial. We performed a sensitivity analysis using a linear regression model estimating means and 95% CI. Analyses were performed using SAS© software, version 9.4 (SAS Institute, Cary, NC).

Results

Sample characteristics

Of the 358 eligible respondents, 285 were included in our analysis. Individuals excluded were missing ADI scores and they were similar to individuals included (Supplemental Table 1 & 2). Overall, almost half reported being diagnosed with an early-stage breast cancer, 40% of respondents reported their race as BIPOC, and 69% had an income of $50,000 or less (Table 1). A total of 40 (14%) of individuals lived in areas of higher disadvantage and 15% reported they had participated in a breast cancer clinical trial. When compared to respondents who lived in areas of lower disadvantage, those in higher

disadvantaged areas were more often Black or African American (55% vs 26%, V: 0.23) and had lower annual income (less than $50K: 83% vs 67%, V: 0.12).

Willingness to participate to a future clinical trial

Participation in a breast cancer clinical trial was similar for individuals living in both areas of higher and lower disadvantage (13% vs 15%, V: 0.03; Table 1). In Figure 1, individuals reported their baseline willingness to participate in a clinical trial with two-thirds (63%) reporting they were somewhat (30%) or very willing (33%) to participate. Additionally, 27% were undecided in their willingness to participate in a cancer clinical trial. The systems-level changes viewed most favorably were having medications delivered to one's home with 49% of respondents reporting they would be very willing to participate, 42% complete online questionnaires, and 40% sign online consent forms (Figure 2). The proportion of the total variance for each type of trial modification from the PCA were all above 0.70: location changes (0.76), telemedicine changes (0.86), convenience changes (0.75), opting out of procedure changes (0.88). Additionally, the range of the loadings were as follows: location changes (0.80-0.91), telemedicine changes (0.89-0.95), convenience changes (0.83-0.89), opting out of procedure changes (both loadings were 0.94).

Probability of being willing to participate in a trial with systems-level change

In our adjusted model, when compared to patients living in lower disadvantaged areas, respondents in higher disadvantaged areas had similar probability of being willing to participate given all systems-level changes (Table 2). However, respondents in higher

versus lower disadvantaged areas had 24% lower probability of being willing to participate due to location changes (RR 0.76, 95% CI 0.51-1.13). Additionally, when compared to patients who had participated in a breast cancer clinical trial, patients who had never participated had higher probability of being willing to participate given all changes: location changes had two times higher probability of being willing to participate, 80% higher probability for telemedicine changes, 47% higher probability for convenience, and 20% higher probability for opting out procedures (all but opting out were statistically significant). Our sensitivity analysis results were consistent with these findings (Supplemental Table 3).

Discussion

The most important finding of our analysis was that individuals who reported no prior participation in breast cancer clinical trials would be more willing to participate in a breast cancer clinical trial given systems-level changes. According to the Friends of Cancer Research preliminary findings, sponsors of trials self-reported flexible modifications did not have a great impact on data integrity.[15] Also, sponsors are continuing to include flexibilities in trials as they see fit. Furthermore, these modifications can reduce burden on sites that conduct trials and patients who participate in them. As sponsors, sites, and patients all view these modifications positively, there is potential that continuing to include trial modifications that increase flexibility will in turn increase cancer clinical trial participation.

Additionally, we found that individuals who were in higher disadvantaged areas had similar probability of being willing to participate in trials with system-level changes

compared to those in lower disadvantaged areas. As individuals who live in areas of higher disadvantage are underrepresented in clinical trials, based on our study, these changes to clinical trials could increase participation in clinical trials. Furthermore, utilizing these clinical trial modifications could decrease patients' time toxicity. Gupta et al conceptualized this concept as the time the patient spends completing the extracurricular items within cancer care, including care coordination (e.g., making appointments, picking up medication), visits plus associated travel and wait time, and potential emergency department or hospital admissions.[16] They found that oftentimes time toxicity is higher in typical cancer clinical trials compared to receiving non-trial treatment; therefore, clinical trials modifications could be beneficial to reducing the burden of time toxicity for participating patients. Future research would need to be conducted to understand how underrepresented patient populations who participate in modified trials view their trial experience, if there are reductions in time toxicity, and the associated benefits.

The system-level change to clinical trials that was viewed most favorably was medications being delivered to one's home with over half of our study sample reporting greater willingness to participate in a trial that offered this option. Research has found that there are benefits for patients receiving mail order drugs. For example, when assessing diabetic drug delivery via mail order or local pharmacy, one study found that for those receiving drugs via mail order had fewer emergency department visits.[17] However, there are concerns surrounding its use. According to Rupp, Medicare-eligible, US rural survey respondents were more concerned about the potential of lost/stolen medication, incorrect medication sent, and environmental effects altering the medication

(e.g., heat, cold) compared to non-rural respondents. Furthermore, most respondents reported a major downside of medications delivered by mail being the lack or loss of relationship with the pharmacist.[18] Royce et al found that almost half of oncology practices reported mail order drugs resulted in drug waste.[19] While we speculate that drug waste would be minimal in a trial environment and patients would still be seeing their cancer provider, these concerns should be considered when designing future clinical trials. Overall, including mail delivery medications in trials could increase participation in trials through the decrease of travel to pick up medications.

Our survey respondents also viewed the increased use of telemedicine in cancer clinical trials favorably. A recent study by Patel et al found that among patients receiving treatment for their cancer, telehealth utilization was associated with savings in patients' time and travel costs.[20] These time and travel cost savings directly impact a patient's financial burden/hardship often seen during cancer care. According to a study by Park et al using the Medical Expenditure Panel Survey, they found that patients with cancer have four times higher mean expenditures compared to individuals without cancer (~$16,000 vs ~$4000).[21] This is especially important for visits a patient may have that neither the trial sponsor nor their insurance payer will cover. Costs that are covered by insurance provider include costs associated with treating the cancer: doctor visits, hospital stays, treatments associated with side effects from cancer drugs, labs, and imaging. However, costs and patient share of the cost will vary depending on type of insurance and hospital. Research costs are not covered by insurance; these include the study drug, and labs and imaging associated with the trial.[22] Research costs may be covered by the trial sponsor, but not always. Ultimately, the use of telemedicine within clinical trials has the ability to

improve patients' quality of life through the not only decreased financial burden but also increased time to spend on their own interests.[23]

One strength of our study is that there is little known on the views on cancer clinical trial modifications from underrepresented patient populations. However, this study should be viewed in light of several limitations. As this uses survey data and is cross-sectional, causal inferences cannot be made. Our sample contained socioeconomically vulnerable breast cancer survivors who had received services from PAF. Therefore, they may not represent the entire cancer population. Additionally, the questions asked regarding participation were hypothetical and patients may change their minds when offered clinical trial participation depending on their life's circumstances.

Conclusions

Cancer clinical trials that include system-level changes are viewed positively by socioeconomically vulnerable patients with breast cancer, specifically those who have not previously participated in trials. Additionally, patients living in higher disadvantaged areas, an underrepresented patient population, were equally willing to participate as individuals in lower disadvantaged areas. Systems-level trial modifications have the potential to increase clinical trial participation.

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Figure legend

Figure 1. Crude proportions of Likert score values for baseline willingness to participate in a breast cancer clinical trial (N=285).

Figure 2. Crude proportions of Likert score values for individual questions surrounding willingness to participate in breast cancer clinical trials (N=285).

Table 1. Demographics and clinical characteristics of overall sample, (N=285) by respondents who lived in areas of lower disadvantage (n=245) and areas of higher disadvantage (n=40).

	Total **N=285**	**Respondents who lived in areas of lower disadvantage** **n=245**	**Respondents who lived in areas of higher disadvantage** **n=40**	**Cramer's V or Cohen's d effect sizes**
	n (%)			
Age at diagnosis in years				0.01
49 or younger	145 (50.9)	125 (51.0)	20 (50.0)	
50 or older	140 (49.1)	120 (49.0)	20 (50.0)	
Race				0.23
American Indian/Alaska Native	1 (0.4)	1 (0.4)		
Asian	7 (2.5)	7 (2.9)		
Black or African American	85 (29.8)	63 (25.7)	22 (55.0)	
More than one race	8 (2.8)	7 (2.9)	1 (2.5)	
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)		
Other	12 (4.2)	11 (4.5)	1 (2.5)	
White/Caucasian	171 (60.0)	155 (63.3)	16 (40.0)	
Ethnicity				0.09
Hispanic or Latino(a) origin or descent	31 (10.9)	24 (9.8)	7 (17.5)	
Non-Hispanic or Latino(a) origin or descent	254 (89.1)	221 (90.2)	33 (82.5)	
Education level				0.10
High school or less	55 (19.3)	46 (18.8)	9 (22.5)	
Some college	124 (43.5)	103 (42.0)	21 (52.5)	
Bachelor's degree or greater	106 (37.2)	96 (39.2)	10 (25.0)	
Annual household income				0.12
$49,000 or less	196 (68.8)	163 (66.5)	33 (82.5)	
$50,000 or more	89 (31.2)	82 (33.5)	7 (17.5)	
Employment status				0.03
Disabled	83 (29.1)	70 (28.6)	13 (32.5)	

Employed	108 (37.9)	94 (38.4)	14 (35.0)	
Retired	55 (19.3)	47 (19.2)	8 (20.0)	
Unemployed/Other	39 (13.7)	34 (13.9)	5 (12.5)	
Breast cancer stage				0.07
Early	152 (53.3)	127 (51.8)	25 (62.5)	
Late	133 (46.7)	118 (48.2)	15 (37.5)	
Years since cancer diagnosis				0.05
Less than 5 years ago	208 (73.0)	177 (72.2)	31 (77.5)	
5-10 years ago	35 (12.3)	30 (12.2)	5 (12.5)	
More than 10 years ago	42 (14.7)	38 (15.5)	4 (10.0)	
Travel time to appointment to see your breast cancer provider (who you see most regularly)				0.08
Less than 30 minutes	170 (59.7)	146 (59.6)	24 (60.0)	
30-60 minutes	76 (26.7)	63 (25.7)	13 (32.5)	
1 hour or greater	39 (13.7)	36 (14.7)	3 (7.5)	
Previously or currently participated in a clinical trial				0.03
Yes	42 (14.7)	37 (15.1)	5 (12.5)	
No	243 (85.3)	208 (84.9)	35 (87.5)	
Breast cancer provider ever discussed a breast cancer clinical trial with respondent				0.01
Yes	81 (28.4)	70 (28.6)	11 (27.5)	
No	204 (71.6)	175 (71.4)	29 (72.5)	

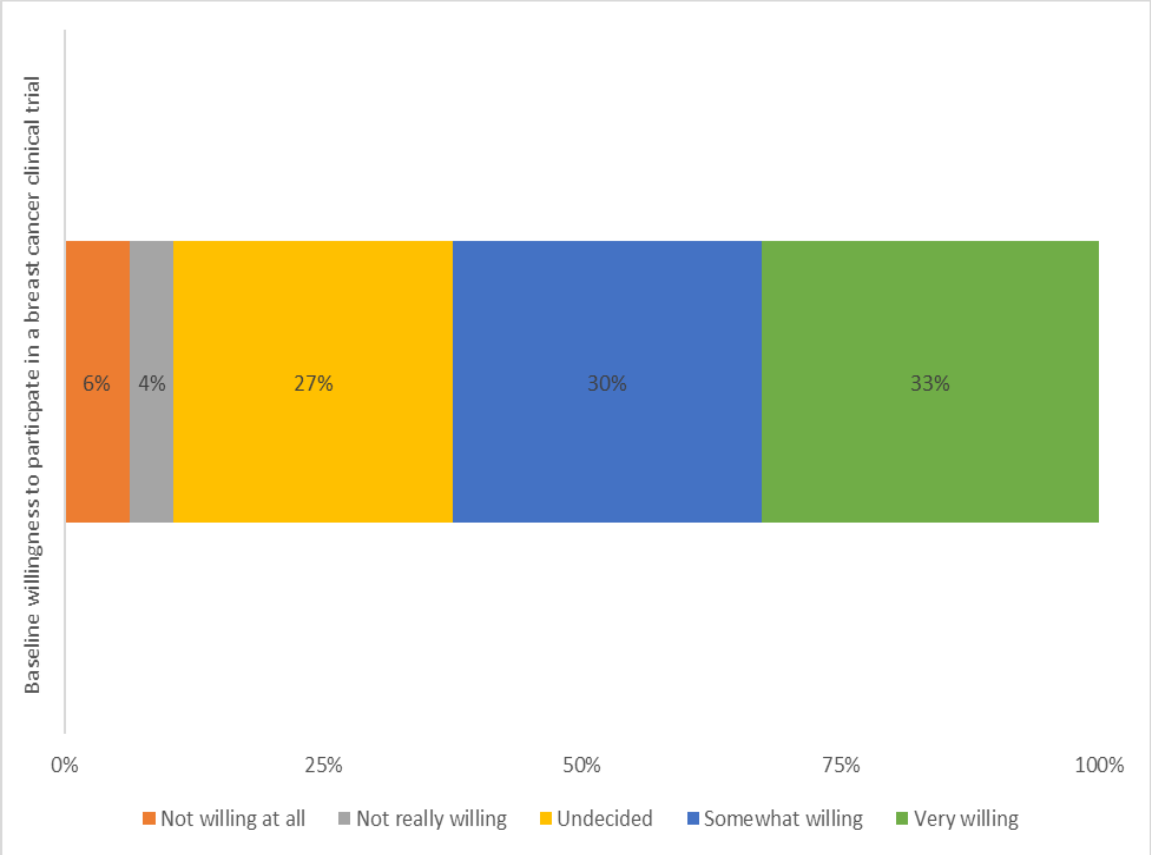
Baseline and willingness to participate values are 1 to 5 point Likert scale.

Table 2. Model-estimated risk ratios, 95% confidence intervals, predicted probabilities evaluating the association between the interaction of Area Deprivation Index & trial participation and the willingness to participate in a clinical trial based on certain changes (N=285).

	Risk ratios (95% CI)	**Predicted probabilities (95% CI)**
Location changes		
Higher disadvantaged	0.76 (0.51-1.13)	0.35 (0.24-0.51)
Lower disadvantaged	Reference	0.46 (0.40-0.53)
Never participated	**2.08 (1.39-3.12)**	0.49 (0.43-0.56)
Previously participated	Reference	0.24 (0.16-0.35)
Telemedicine changes		
Higher disadvantaged	1.00 (0.78-1.28)	0.55 (0.43-0.69)
Lower disadvantaged	Reference	0.55 (0.49-0.61)
Never participated	**1.81 (1.34-2.46)**	0.60 (0.54-0.66)
Previously participated	Reference	0.33 (0.24-0.45)
Convenience changes		
Higher disadvantaged	1.08 (0.85-1.39)	0.58 (0.46-0.73)
Lower disadvantaged	Reference	0.54 (0.48-0.60)
Never participated	**1.47 (1.09-2.00)**	0.57 (0.51-0.64)
Previously participated	Reference	0.39 (0.29-0.52)
Opting out of procedure changes		
Higher disadvantaged	0.96 (0.67-1.38)	0.45 (0.32-0.64)
Lower disadvantaged	Reference	0.47 (0.41-0.54)
Never participated	1.20 (0.85-1.70)	0.48 (0.42-0.55)
Previously participated	Reference	0.40 (0.29-0.56)

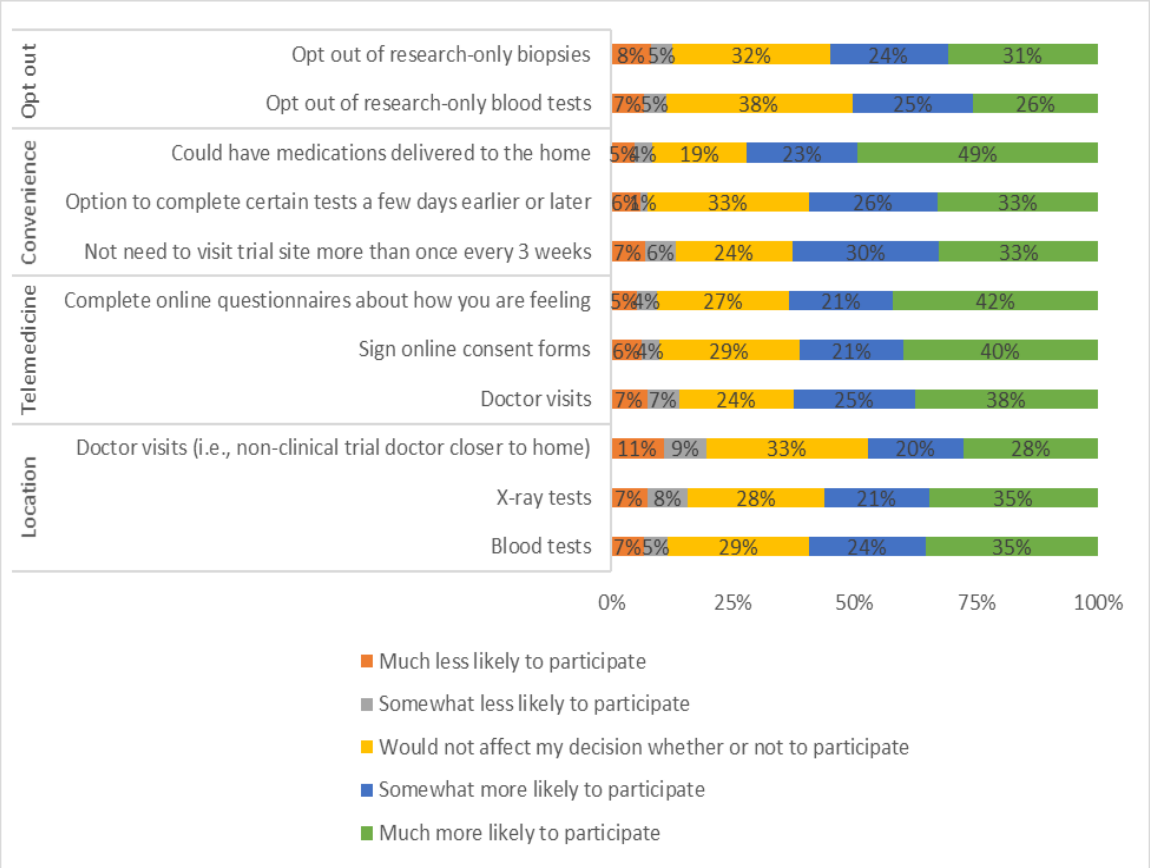
Baseline and willingness to participate values are 1 to 5 Likert scale. Higher scores represent more willingness to participate in a cancer clinical trial based on given trial change. Models were adjusted for age at diagnosis, race, ethnicity, cancer stage, travel time to cancer center, and baseline willingness to participate in a clinical trial. Bolded values represent significance at the alpha level of 0.05. CI=confidence intervals.

Figure 1. Crude proportions of Likert score values for baseline willingness to participate in a breast cancer clinical trial (N=285).



Baseline willingness to participate values are 1 to 5 Likert scale. Higher scores represent more willingness to participate in a cancer clinical trial.

Figure 2. Crude proportions of Likert score values for individual questions surrounding willingness to participate in breast cancer clinical trials (N=285).



Willingness to participate values are 1 to 5 Likert scale. Higher scores represent more willingness to participate in a cancer clinical trial based on given trial change. A score of 3 means change would not affect willingness to participate.

Supplemental Table 1. Demographic and clinical characteristics of respondents included (N=258) and not excluded from our analysis (N=73).

	Included in the analysis N=285	**Excluded from the analysis N=73**	**Cramer's V or Cohen's d**
	n (%)		
Age at diagnosis in years			0.04
49 or younger	145 (50.9)	41 (56.2)	
50 or older	140 (49.1)	32 (43.8)	
Race			0.08
American Indian/Alaska Native	1 (0.4)		
Asian	7 (2.5)	3 (4.1)	
Black or African American	85 (29.8)	17 (23.3)	
More than one race	8 (2.8)	3 (4.1)	
Native Hawaiian or Other Pacific Islander	1 (0.4)		
Other	12 (4.2)	4 (5.5)	
White/Caucasian	171 (60.0)	46 (63.0)	
Ethnicity			0.00
Hispanic or Latino(a) origin or descent	31 (10.9)	8 (11.0)	
Non-Hispanic or Latino(a) origin or descent	254 (89.1)	65 (89.0)	
Education level			0.06
High school or less	55 (19.3)	10 (13.7)	
Some college	124 (43.5)	33 (45.2)	
Bachelor's degree or greater	106 (37.2)	30 (41.1)	
Annual household income			0.02
Less than $50,000	196 (68.8)	52 (71.2)	
$50,000 or more	89 (31.2)	21 (28.8)	
Employment status			0.08
Disabled	83 (29.1)	26 (35.6)	
Employed	108 (37.9)	24 (32.8)	
Retired	55 (19.3)	11 (15.1)	
Unemployed/Other	39 (13.7)	12 (16.4)	
Area Deprivation Index			
Less disadvantaged	245 (86.0)		
More disadvantaged	40 (14.0)		
Breast cancer stage			0.00
Early	152 (53.3)	39 (53.4)	
Late	133 (46.7)	34 (46.6)	
Years since cancer diagnosis			0.10

Less than 5 years ago	208 (73.0)	53 (72.6)	
5-10 years ago	35 (12.3)	14 (19.2)	
More than 10 years ago	42 (14.7)	6 (8.2)	
Travel time to appointment to see your breast cancer provider (who you see most regularly)			0.08
Less than 30 minutes	170 (59.6)	45 (61.6)	
30-60 minutes	76 (26.7)	14 (19.2)	
1 hour or greater	39 (13.7)	14 (19.2)	
Previously or currently participated in a clinical trial			0.02
Yes	42 (14.7)	12 (16.4)	
No	243 (85.3)	61 (83.6)	

Supplemental Table 2. Crude means and standard deviations of willingness to participate in trials questions of individuals included (N=285) and excluded in our analysis (N=73).

	Included in the analysis N = 285	**Excluded from the analysis N=73**	**Cohen's d effect sizes**
	Mean (standard deviation)		
Baseline willingness to participate in a clinical trial	3.78 (1.14)	3.86 (1.16)	0.07
Overall location change questions	3.63 (1.07)	3.64 (1.13)	0.01
Blood tests	3.76 (1.80)	3.81 (1.21)	0.04
X-ray tests	3.68 (1.24)	3.64 (1.24)	0.03
Doctor visits (i.e., non-clinical trial doctor closer to home)	3.45 (1.28)	3.47 (1.17)	0.02
Overall telemedicine changes questions	3.85 (1.00)	3.83 (1.01)	0.02
Doctor visits	3.79 (1.22)	3.82 (1.16)	0.03
Sign online consent forms	3.85 (1.17)	3.79 (1.14)	0.05
Complete online questionnaires after how you are feeling	3.91 (1.15)	3.85 (1.09)	0.05
Overall convenience changes questions	3.88 (0.98)	3.85 (0.98)	0.02
Not need to visit trial site more than once every 3 weeks	3.75 (1.18)	3.70 (1.13)	0.04
Option to complete certain test a few days earlier or later	3.79 (1.10)	3.71 (1.10)	0.07
Could have medications delivered to the home	4.08 (1.13)	4.15 (1.13)	0.06
Overall opt-out changes questions	3.62 (1.08)	3.44 (1.16)	0.16
Opt out of research-only blood tests	3.58 (1.12)	3.45 (1.19)	0.12
Opt out of research-only biopsies	3.65 (1.19)	3.42 (1.25)	0.19

Baseline and willingness to participate values are 1 to 5 Likert scale. Higher scores represent more willingness to participate in a cancer clinical trial based on given trial change. A score of 3 means change would not affect willingness to participate.

Supplemental Table 3. Linear regression sensitivity analysis: Model-estimated means and 95% confidence intervals evaluating the association between the interaction of Area Deprivation Index & trial participation and the willingness to participate in a clinical trial based on certain changes (N=285).

	Means (95% CI)
Location changes	
Participated in a clinical trial	2.90 (2.56-3.24)
Never participated	3.75 (3.63-3.88)
Higher disadvantaged	3.55 (3.24-3.87)
Lower disadvantaged	3.64 (3.52-3.76)
Telemedicine changes	
Participated in a clinical trial	3.14 (2.80-3.48)
Never participated	3.97 (3.85-4.10)
Higher disadvantaged	3.95 (3.63-4.27)
Lower disadvantaged	3.83 (3.71-3.96)
Convenience changes	
Participated in a clinical trial	3.46 (3.15-3.76)
Never participated	3.95 (3.83-4.06)
Higher disadvantaged	3.86 (3.57-4.14)
Lower disadvantaged	3.88 (3.77-3.99)
Opting out of procedure changes	
Participated in a clinical trial	3.37 (3.03-3.72)
Never participated	3.66 (3.53-3.79)
Higher disadvantaged	3.61 (3.28-3.93)
Lower disadvantaged	3.62 (3.49-3.75)

Higher scores represent more willingness to participate in a cancer clinical trial based on given trial change. A score of 3 means change would not affect willingness to participate. Models were adjusted for age at diagnosis, race, ethnicity, education level, annual household income, employment status, cancer stage, travel time to cancer center, and baseline willingness to participate in a clinical trial. CI=confidence intervals.

Supplemental Figure. Survey questions.

You are being asked to complete an online research survey from Patient Advocate Foundation. We are conducting this research because we want to learn how people feel about participating in breast cancer clinical trials.

Breast cancer clinical trials are a type of research done to learn about breast cancer and about how to improve breast cancer treatments. Your responses to this survey will build on prior research about barriers to clinical trial participation and may help breast cancer researchers improve how they conduct breast cancer clinical trials during and after the pandemic.

This survey was deemed exempt by the University of Alabama at Birmingham Institutional Review Board. Completing this survey is optional and your answers will be kept anonymous. By beginning this survey, you are providing consent to participate in this research.

This survey will take approximately 15 minutes of your time. Please mark only one answer for each question unless otherwise indicated.

Individuals who complete the entire survey will be entered into a drawing to win <u>one</u> of five digital $100 Amazon gift cards. Winners will be notified via email by Patient Advocate Foundation.

1. I agree to participate in this survey.
    - Yes
    - No

2. Have you ever been diagnosed with breast cancer?
    - Yes
    - No
3. How many years ago were you first diagnosed with breast cancer?
    - Less than 1 year ago
    - 1-5 years ago
    - 5-10 years ago
    - More than 10 years ago
4. Which of the following statements most accurately describes you?
    - I have been diagnosed with early stage breast cancer (breast cancer involving the breast with or without involving the armpit lymph glands)
    - I have been diagnosed with metastatic breast cancer (breast cancer that has spread to other parts of the body)
    - Other
5. Are you at least 18 years of age?
    - Yes
    - No
6. Where do you live?
    - United States
    - Another country besides United States
7. Have you ever participated in a breast cancer clinical trial?
    - Yes
    - No

8. Are you currently participating in a breast cancer clinical trial?
    - Yes
    - No

People who participate in breast cancer clinical trials often have to attend appointments and have to undergo treatments, x-ray tests, biopsy procedures and laboratory tests, many of which are done at the cancer clinic conducting the clinical trial. Some of the tests affect breast cancer care while others are done for research purposes only.

During the COVID-19 pandemic, researchers have cut back or changed requirements for people participating in clinical trials. Some researchers think these changes should continue after the pandemic also.

Please tell us whether the following changes would affect your decision to participate in a clinical trial during or after the COVID-19 pandemic. If you are currently participating in a clinical trial, please indicate whether the following changes would affect your decision to participate in another clinical trial during or after the COVID-19 pandemic.

9. CHANGE LOCATION: If you could complete the following trial requirements at a location close to your home instead of traveling to the clinical trial site to do them, how would this affect your decision to participate?

	Much less likely to participate	Somewhat less likely to participate	Would not affect my decision whether or not to participate	Somewhat more likely to participate	Much more likely to participate
Blood tests					
X-ray tests					
Doctor visits (i.e. you would see a doctor close to home who **is not involved in the clinical trial** instead of the clinical trial doctor)					

10. SWITCH CLINICAL TRIAL PROCEDURES TO SECURE TELEMEDICINE PORTAL: If you could complete the following trial requirements electronically instead of traveling to the clinical trial site to do them in person, how would this affect your decision to participate?

	Much less likely to participate	Somewhat less likely to participate	Would not affect my decision whether or not to participate	Somewhat more likely to participate	Much more likely to participate
Doctor visits (i.e. you would see the clinical trial doctor via telemedicine using phone or video connection)					
Sign online forms to consent to participate in the trial					
Complete online questionnaires about how you are					

feeling					

11. MAKING TRIAL SCHEDULE FLEXIBLE AND CONVENIENT: If the following aspects of the clinical trial were flexible and convenient, how would it affect your decision to participate?

	Much less likely to participate	Somewhat less likely to participate	Would not affect my decision whether or not to participate	Somewhat more likely to participate	Much more likely to participate
I would not need to come to the clinical trial site more frequently than once every 3 weeks					
I could opt out of blood tests for the clinical trial that are for research only (i.e. that do not affect my care)					

I could opt out of biopsies for the clinical trial that are for research only (i.e. that do not affect my care)					
Rather than completing doctor visits, treatments, tests or procedures for the clinical trial on a specific day, I could have the option of completing them a few days earlier or a few days later					
Rather than coming to the clinical trial site to pick up medications taken by mouth for the					

clinical trial, I could have the medications delivered to my home					

12. What is your race? Check all that apply.

- American Indian/Alaska Native
- Asian
- Black/African American
- Native Hawaiian or Other Pacific Islander
- White/Caucasian
- Other

13. Are you of Hispanic or Latino(a) origin or descent?

- Yes
- No

14. Please indicate your highest level of academic achievement:

- Less than a high school diploma or equivalent
- High school diploma or equivalent
- Some college, no degree
- Associate's degree
- Bachelor's degree
- Master's or doctoral degree

15. Please indicate your current household income per year in US dollars.

- Less than $20,000
- $20,000 to $34,999
- $35,000 to $49,999
- $50,000 to $74,999
- $75,000 to $99,999
- More than $100,000

16. What is your current employment status? Please select what you consider to be your main activity.

- Working full time (≥32 hours/week)
- Working part time (1-31 hours/week)
- Unemployed, looking for work
- Unemployed, not looking for work
- In job training
- Temporarily laid off (no pay)
- Retired
- On short term disability
- On long term disability
- Permanently disabled
- I do not work
- In school
- Other

17. Please indicate your health insurance type. Pease select all that apply.

- Private (e.g. BlueCross, Cigna)
- Medicare
- Medicaid
- Tri-Care/Other Military
- Indian Health Service
- The Veterans Health Administration (VA)
- None
- Other

18. How old were you when you were first diagnosed with breast cancer?

- Under 18
- 18-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70 or older

19. How long does it take for you to travel to an appointment to see your breast cancer provider? If you have more than one breast cancer provider, please indicate the time it takes for you to travel to an appointment with the provider you see the most frequently.

- Less than 15 minutes
- 15-30 minutes

- 30-60 minutes
- 60-90 minutes
- More than 90 minutes

UNDERSTANDING PATIENT-LEVEL FACTORS THAT INFLUENCE PARTICIPATION IN A BREAST CANCER CLINICAL TRIAL

by

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Abstract

Background: Though cancer clinical trials offer novel treatments, participating patients do not represent populations seen in clinic. It is unclear how patient sociodemographics, attitudes, and knowledge about clinical trials influence breast cancer (BC) clinical trial participation.

Methods: This cross-sectional analysis used survey data collected in 12/2022 by Patient Advocate Foundation (PAF) among women who had previously received PAF services and had a BC diagnosis. Respondents reported BC clinical trial participation, Attitudes Toward Cancer Trials Scale, clinical trial knowledge, age at diagnosis, race, education level, annual household income, employment status, and BC stage. Descriptive and bivariate analyses were conducted using Cramer's V or Cohen's d as effect sizes. Standardized total effects (b_{Tot}) were estimated using a pre-specified Structural Equation Model with 0.1, 0.3, and 0.5 indicating weak, medium, and large magnitude, respectively.

Results: Of 358 respondents, 39% were Black, Indigenous, or a Person of Color, 38% had ≥Bachelor's degree, and 69% had incomes <$50,000. Overall, knowledge was low (mean 3.5 of 7, standard deviation (SD) 1.9). Respondents who reported trial participation (15%) more often had positive attitudes toward trials (mean 88 of 126, SD 23.3 vs 83, SD 15.6; d 0.29) compared to those not reporting participation. Positive attitude was a stronger antecedent to trial participation than knowledge (b_{Tot} = 0.13, p=0.01 vs. b_{Tot} = 0.06, p=0.28). However, knowledge was an antecedent of attitudes (b_{Tot} = 0.15, p=0.003).

Discussion: Future interventions to increase and diversify enrollment should focus on promotion of positive attitudes towards clinical trials, potentially through increased trial knowledge.

Background

Cancer clinical trials are not representative of real-world populations seen in clinical practice.[1,2] In our prior research among patients at our institution, we found that patients living in areas of higher versus lower disadvantage had 3.4 times the odds of declining enrollment when directly offered to participate, despite having had similar odds of being interested, eligible, and offered a trial by a provider.[3] There is a lack of knowledge as to why this particular patient population has lower enrollment percentages than patients living in areas of lower disadvantage.

One limitation of that analysis was the use of area-level information on factors such as education, income, and employment, which are valuable for group characteristics, but may not represent patient-level characteristics.[4,5] There are many reasons underrepresented patients do not participate in clinical trials including logistical, financial, and societal reasons;[6] it is unknown which patient-level factor is the greatest contributor to clinical trial participation, especially among socioeconomically vulnerable patients.

Attitudes and knowledge are very important within decision-making. According to Sanbonmatsu and Fazio, while knowledge of a subject can allow for a more deliberate choice, they found that individuals often do not use their readily available knowledge, instead focus on their attitudes to make an effortless choice.[7] When faced with deciding to participate in a cancer clinical trial, little is known about the interplay between these patient-level factors and one's own attitudes toward and knowledge of clinical trials. This is especially important following the COVID-19 pandemic, during which both the healthcare system underwent changes and individual-level views of science altered.[8,9]

Therefore, the purpose of this study aimed to understand which patient-level factor influences clinical trial participation in breast cancer clinical trials among socioeconomically vulnerable individuals. Furthermore, to better understand what influences attitudes toward clinical trials, we also assessed the relationship between patient-level demographics and attitudes.

Methods

Study design and participants

This cross-sectional study used survey data from a nationwide cohort of female respondents with breast cancer. This survey was fielded from 12/06/2022 through 12/31/2022 by Patient Advocate Foundation (PAF) to individuals who were recently served by PAF. PAF is a nationwide nonprofit organization that provides social needs navigation and financial aid to patients diagnosed with a chronic illness. Patients seeking services from PAF face healthcare access and affordability challenges: many of our respondents represent marginalized populations, face a variety of social needs, and are limited in the resources they have available to meet both medical and non-medical needs.[10] Inclusion criteria included female sex with a diagnosis of breast cancer at any stage within the last five years or metastatic breast cancer at any time, the ability to complete the survey in English, aged > 18 years of age, and US residence. All survey questions were required to ensure complete data capture. We sent additional survey reminders to individuals who lived in higher disadvantaged areas and who had previously self-reported their race as Black, Indigenous, or a Person of Color (BIPOC) to elicit more responses from individuals who are typically underrepresented in clinical trials. Conduct

of this study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB-300010015).

Outcomes

Participation in a clinical trial: The following question was asked, "Have you ever participated in a breast cancer clinical trial?" Responses were yes or no for these questions. The supplemental figure contains all survey questions.

Variables of interest for Structural Equation Modeling

Patient-level education level: Education level was self-reported by survey respondents and grouped into high school diploma or less (less than high school, high school); some college (some college, Associate's degree); and Bachelor's degree or more (Bachelor's, Master's, Doctorate degree). For Structural Equation Modeling (SEM), years of education were used as follows: 9 years (less than high school), 12 (high school), 13 (some college), 14 (Associate's degree), 16 (Bachelor's degree), and 18 (Master's or Doctorate degree).

Patient-level annual household income: Survey respondents reported their annual household income and was grouped into less than $50,000 and $50,000 or more. For SEM, we grouped income values by the median income of the given category ($10k, $28k, $43k, $58k, $83k, $110k).

Patient-level employment status: The following employment status groups were included in our analysis: employed (working either part or full time [32 hours or more/week]), unemployed/other (unemployed, temporarily laid off, do not work, student, other),

retired/disabled (retired, on short- or long-term disability, permanently disabled). We grouped retired/disabled as we these individuals are receiving some income.

Attitudes Toward Cancer Trials Scale: Using an 18-tem questionnaire developed by Schuber and colleagues, we determined individual attitudes toward clinical trials.[11] All responses are on a 7-point Likert scale [1) strongly disagree, 2) disagree, 3) somewhat disagree, 4) neither agree nor disagree, 5) somewhat agree, 6) agree, 7) strongly agree]. Scores range from 18-126, with higher scores indicating more positive attitudes. We also categorized this into two groups depending on the mid-point of responses; groups were considered as having positive leaning or negative-leaning attitudes. Personal beliefs and trust in the research process subscales range from 4-28; personal barriers and safety and personal and social value subscales range from 5-35. Personal barriers and safety score is kept negative coded for subscale but reverse coded for the overall score.

Knowledge about clinical trials: To understand knowledge of clinical trials, we used a 7-item questionnaire developed by Ellis and colleagues. Scores range from 0-7 and correct responses are given one point; higher scores indicated more knowledge about clinical trials.[12,13] We further categorized knowledge into two groups as having more knowledge (scores 5, 6, 7) vs less knowledge (scores 4 or less). We choose the score of 4 because if a test, it would be considered a failing grade (57% of correct answers).

Cancer stage: Cancer stage was grouped as early (with or without lymph node involvement) or late (having spread to other parts of the body) and was self-reported by survey respondents.

Additional variables of interest

Respondents also self-reported age at diagnosis (49 years or younger, 50 or older), race (American Indian/Alaska Native, Asian, Black/African American, more than one race, Native Hawaiian or Pacific Islander, other, White/Caucasian), ethnicity (Hispanic or Latino(a) or non-Hispanic or Latino(a) origin or descent), and years since cancer diagnosis (less than five years ago, 5-10 years ago, more than ten years ago). Additionally, insurance was grouped into having Medicaid, Medicare, none/other/unknown, or private. Finally, individuals were asked if a breast cancer provider had ever discussed a breast cancer clinical trial with them and responses were grouped as yes or no.

Statistical analysis

Descriptive statistics were calculated using frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. Differences in characteristics for respondents who had and had not participated were calculated using measures of effect size such as Cohen's d (i.e., the standardized mean difference; small: 0.2, medium: 0.5, large: 0.8) for numerical characteristics or Cramer's V for cross-tabulations. V of 0.1 is considered a small effect, 0.3 a medium effect, and 0.5 a large effect when comparing across two categories; 0.1 a small effect, 0.25 a medium effect, and 0.4 a large effect when comparing across more than two categories.[14] We used Structural Equation Modeling to fit a pre-specified path model for patient characteristics as they influence clinical trial enrollment. We estimated our pre-specified SEM model and evaluated fit using an estimator robust to non-normality. Appropriate model fit was

determined using the Root Mean Squared Error of Approximation (RMSEA) index. Values less than 0.06 indicate good model fit, values from 0.06-0.1 indicate fair fit, and values greater than 0.1 indicate poor fit.[15,16] Using the estimated path coefficients, standardized direct, indirect, and total effects were estimated on the likelihood of clinical trial enrollment. The standardized path coefficients and effects were interpreted as standardized regression coefficients: 0.1 weak, 0.3 medium, and 0.5 large associations. We fitted an exploratory logistic regression model estimating the odds ratios (OR), predicted probabilities, and 95% confidence intervals (CI) assessing the interaction between attitudes and knowledge on having ever participated in a breast cancer clinical trial. This model was controlled for age at diagnosis, race (due to small numbers, categories with less than 20 individuals were grouped into a singular group for modeling purposes), ethnicity, cancer stage, education, employment, and income. We fitted an additional exploratory logistic regression model examining the association between various patient-level demographics and positive-leaning attitudes toward clinical trials. The statistical significance level was set to 0.05. Analyses were performed using SAS© software, version 9.4 (SAS Institute, Cary, NC). PROC CALIS was used for fitting the path model.

Results

Sample characteristics

Our study included 358 eligible female breast cancer survivors; we were able to include all respondents in our analysis and due to survey structure there were no missing data. Overall, 39% were BIPOC, 62% had lower than a Bachelor's degree, 69% had an annual

household income of less than $50,000, and almost half (49%) were retired or disabled (Table 1). A total of 54 (15%) respondents had participated in a breast cancer clinical trial. Compared to those who had not participated, individuals who participated in a clinical trial more often had a Bachelor's degree or higher (50% vs 36%, V: 0.12) and income greater than $50,000 (39% vs 29%, V: 0.07). Additionally, about one in six individuals who did not participate in a breast cancer clinical trial reported a provider did discuss a clinical trial with them. Overall, knowledge of clinical trials was low (means score 3.5 of 7 [SD: 1.94]) and attitudes toward clinical trials were mostly positive leaning (75%). Additionally, mean clinical trial knowledge scores and attitudes toward clinical trials varied between respondents who participated or not. Individuals who had participated vs not had higher knowledge (mean 3.9 (SD 1.7) vs 3.5 (2.0); d: 0.23) and more positive attitudes (87.8 (23.3) vs 82.9 (15.6), d: 0.29).

Influence of demographics on breast cancer clinical trial participation

Figure 1 contains our initial hypothesized path model. Our initial path had good fit with a RMSEA of 0.02 (Figure 2). Though all variables in our model had modest associations with participation in a breast cancer clinical trial (standardized coefficients <0.30), the factor that had the most influence was the Attitudes Toward Cancer Trials (standardized direct effect 0.13, p-value 0.01, Table 2). Additionally, knowledge of clinical trials had a significant association with attitudes (0.15, p-value 0.003); however, knowledge did not have a significant association with participation in a clinical trial (standardized total effect 0.06, p-value 0.28). Therefore, in our subsequent exploratory logistic model, we were interested in the interaction between knowledge and attitudes on participation in a

breast cancer clinical trial. Of individuals with positive-leaning attitudes, 15% of individuals with both high and low knowledge participated in a breast cancer clinical trial (Figure 3). While of those with negative-leaning attitudes, 4% with high knowledge and 11% with low knowledge participated in a clinical trial. Regardless of knowledge, individuals with positive compared to negative-leaning attitudes had higher odds of participating in a clinical trial, though not statistically significant (High knowledge: OR 4.05; 95% CI 0.50-32.99; low knowledge: OR 1.42; 95% CI 0.60-3.35; Table 3).

Attitudes Toward Clinical Trials and patient-level demographics

For further exploration, we modeled the association between patient-level demographics and positive-leaning attitudes toward cancer trials. Compared to White individuals, a lower odds of positive-leaning attitudes was observed for Black (OR 0.74, 95% CI 0.42-1.29) and other race individuals (OR 0.71, 95% CI 0.32-1.59). Additionally, individuals who reported income of $50,000 or more compared to those reported less than $50,000 had 1.38 times the odds of positive-leaning attitudes (95% CI 0.75-2.56). However, neither of these results were statistically significant.

Discussion

In our study, we found that the attitudes are associated with breast cancer clinical trial participation. There is little research surrounding patients' attitudes toward clinical trials, especially of late (i.e, post-pandemic). In 2020, Lewin et al conducted a study assessing attitudes toward clinical trials of adolescents and young adult (AYAs). [17] Compared to non-AYAs, they found that AYAs viewed clinical trials less favorably;

AYAs reported trials to be unsafe and more difficult as they have more personal barriers to trials. Research has also assessed the publics' and providers' attitudes toward clinical trials. Using telephone interviews, Comis et al found in 2000 that 32% of US adults viewed trials favorably as they reported they would be very willing to participate in trials.[18] Furthermore, in late 2020, Wong et al found through qualitative interviews, that community oncologists felt that patient's attitudes affected their trial participation.[19] While there are data lacking on attitudes towards clinical trials for women with breast cancer, it appears that overall trials are viewed favorably and those attitudes can predict participation.

We also found that our sample of respondents had poor knowledge about cancer clinical trials. In a 1999 study by Ellis et al, patients had low knowledge about clinical trials, with a median score of 3 out of 7, which is similar to what we found.[20] This suggests that knowledge about clinical trials has remained low over a long period of time. Furthermore, we did not find a relationship between knowledge and participation. In 2001, Ellis et al fielded a survey on individuals receiving breast cancer screening; the majority of their sample did not have breast cancer whereas few individuals did have breast cancer. Overall, they found that individuals who were more likely to consider participation in a trial had greater knowledge of clinical trials,[13] which contradicted our results. However, we did find a strong relationship between knowledge and attitudes. While these results point to the potential use of the knowledge-attitude-behavior (KAB) model[21] to change behavior, unfortunately, we feel this may not be the best way to increase participation in cancer clinical trials for this particular group of individuals. We found that even respondents who had low knowledge, those with positive-leaning

attitudes had higher odds of participation compared to patients with negative-leaning attitudes.

Another important finding our study found is that almost three in four individuals reported that a provider did not discuss a breast cancer clinical trial with them. However, NCCN guidelines state that clinical trials are standard of care and discussions are recommended.[22] Furthermore, having a cancer diagnosis can be distressing[23,24] which could lead patients to not recall everything that their providers discussed with them in their appointments. Also, patients may make decisions out of these distressing emotions and may rely heavily on their provider for guidance in choosing to participate in a trial or not.[25,26] Therefore, providers should make discussions about clinical trials distinct and clear. The focus of these conversations should be on trust building between patient and provider, and ultimately the research process, which has the potential to increase clinical trial participation.[27]

We did not find any patient-level socioeconomic demographics nor clinical characteristics to be associated with more positive attitudes to clinical trials. This could be due to our data, as the majority of individuals had positive-leaning attitudes toward clinical trials. However, there are multi-leveled factors that influence attitudes (e.g., experiences, beliefs, feelings, norms, influences)[28] and we recommend future interventions aimed at increasing cancer clinical trial participation using the Integrated Behavior Model (IBM). According to the IBM, there are five items that have a direct effect on one's behavior and to affect change, all must be present. These include knowledge and skills to perform said behavior, salience of behavior, environmental constraints, habit, and intention or decision to perform the behavior; intention is

influenced by various types of beliefs and our feelings about the final behavior.[29] Furthermore, the IBM posits intention to partake in the behavior is the most important cause. Future research is needed to understand the connections between patient-level knowledge in connection with the importance/reasons for participating in a clinical trial, environment (logistical, financial, and societal) they live in that facilities participation, and the habits of those who have participated in a clinical trial vs not. Understanding these factors via more robust study designs and qualitative interviews will be important in creating behavioral interventions to increase participation.

This study should be considered in light of several limitations. This sample of individuals previously sought case management and financial assistance from PAF and therefore may have lower financial resources which may not reflect the total breast cancer population. As this was a cross-sectional study, we cannot make any causal claims. We are unaware if attitudes changed after participating in a trial or if attitudes were a factor for participation. Unfortunately, due to protecting the privacy of individuals, we were unable to include region of respondent residence as this may provide information on access to clinical trials. As this survey captured the individual-level response to clinical trials and not the physician involvement in the trial, we are limited in understanding the full extent of how the provider was involved in the respondent's decision-making for trial participation.

Conclusions

In conclusion, positive attitudes toward cancer clinical trials was associated with breast cancer clinical participation within our sample of socioeconomically vulnerable breast

cancer survivors. As we did not find any patient-level demographics to be associated with attitudes, interventions to increase clinical trial participation should focus on trust building between patient and provider/healthcare system along with behavioral models of change to affect attitudes.

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Figure legend

Figure 1. Hypothesized conceptual model.

Figure 2. Final conceptual model with standardized direct effects (N=358).

Figure 3. Predicted probabilities evaluating the association between both attitudes toward clinical trials and knowledge about clinical trials and participation in a clinical trial (N=358).

Table 1. Patient demographics and clinical characteristics of overall sample, (N=358) by participation in a breast cancer clinical trial (n=54), or not (n=304).

	Total **N=358**	**Participation in breast cancer clinical trial** **n=54 (15%)**	**Never participated in a breast cancer clinical trial n=304 (85%)**	**Cramer's V or Cohen's d**
	n (%)			
Age at diagnosis, in years				0.01
49 or younger	186 (52.0)	29 (53.7)	157 (51.6)	
50 or older	172 (48.0)	25 (46.3)	147 (48.4)	
Race				0.08
American Indian/Alaska Native	1 (0.3)		1 (0.3)	
Asian	10 (2.8)	1 (1.9)	9 (3.0)	
Black/African American	102 (28.5)	17 (31.5)	85 (28.0)	
More than one race	11 (3.1)	1 (1.9)	10 (3.3)	
Native Hawaiian or Pacific Islander	1 (0.3)		1 (0.3)	
Other	16 (4.5)	1 (1.9)	15 (4.9)	
White/Caucasian	217 (60.6)	34 (63.0)	183 (60.2)	
Ethnicity				0.00
Hispanic or Latino(a) origin or descent	39 (10.9)	6 (11.1)	33 (10.9)	
Non-Hispanic or Latino(a) origin or descent	319 (89.1)	48 (88.9)	271 (89.1)	
Education level				0.12
High school or less	65 (18.2)	5 (9.3)	60 (19.7)	
Some college	157 (43.9)	22 (40.7)	135 (44.4)	
Bachelor's degree or more	136 (38.0)	27 (50.0)	109 (35.9)	
Annual household income				0.07
Less than $50,000	248 (69.3)	33 (61.1)	215 (70.7)	
$50,000 or more	110 (30.7)	21 (38.9)	89 (29.3)	
Employment status				0.08
Employed	132 (36.9)	21 (38.9)	111 (36.5)	
Retired/disabled	175 (48.9)	29 (53.7)	146 (48.0)	
Unemployed/Other	51 (14.3)	4 (7.4)	47 (15.5)	
Breast cancer stage				0.09
Early	191 (53.4)	23 (42.6)	168 (55.3)	

Late	167 (46.7)	31 (57.4)	136 (44.7)	
Years since cancer diagnosis				0.10
Less than 5 years ago	261 (72.9)	34 (63.0)	227 (74.7)	
5-10 years ago	49 (13.7)	9 (16.7)	40 (13.2)	
More than 10 years ago	48 (13.4)	11 (20.4)	37 (12.2)	
Insurance				0.06
Ever Medicaid	95 (26.5)	14 (25.9)	81 (26.6)	
Ever Medicare	114 (31.8)	17 (31.5)	97 (31.9)	
None/other/unknown	24 (6.7)	2 (3.7)	22 (7.2)	
Private	125 (34.9)	21 (38.9)	104 (34.2)	
Breast cancer provider discussed a breast cancer clinical trial				0.62
Yes	102 (28.5)	51 (94.4)	51 (16.8)	
No	256 (71.5)	3 (5.6)	253 (83.2)	
Clinical trial knowledge score, mean (SD)	3.5 (1.94)	3.9 (1.66)	3.5 (1.98)	0.23
Clinical trial knowledge categorized				0.01
High knowledge	115 (32.1)	18 (33.3)	97 (31.9)	
Low knowledge	243 (67.9)	36 (66.7)	207 (68.1)	
Attitudes Toward Cancer Trials Scale, mean (SD)	83.7 (17.03)	87.8 (23.25)	82.9 (15.61)	0.29
Personal beliefs subscale score, mean (SD)	15.2 (6.57)	15.0 (6.77)	15.3 (6.54)	0.04
Personal barriers and safety subscale score, mean (SD)*	17.8 (7.1)	16.0 (7.16)	18.1 (7.0)	0.30
Personal and social value subscale score, mean (SD)	26.4 (6.77)	27.7 (8.72)	26.2 (6.35)	0.23
Trust in the research process subscale score, mean (SD)	19.8 (5.49)	21.0 (6.69)	19.5 (5.23)	0.27
Attitudes Toward Cancer Trials Scale categorized				0.08
Positive-leaning attitudes	267 (74.6)	45 (83.3)	222 (73.0)	
Negative-leaning attitudes	91 (25.4)	9 (16.7)	82 (27.0)	

Clinical trial knowledge score ranges from 0-7 with higher scores indicating more knowledge about clinical trials. Knowledge scores equal to or greater than 5 were considered high knowledge, as this would be considered a passing grade. Attitudes Toward Cancer Trials Scale ranges from 18-126 with higher scores indicating more

positive attitudes toward clinical trials. Personal beliefs and trust in the research process subscales range from 4-28; personal barriers and safety and personal and social value subscales range from 5-35. *Personal barriers and safety score is kept negative coded for subscale but reverse coded for overall score. IQR=interquartile range.

Table 2. Model-estimated standardized total, direct, and indirect path coefficients, standard errors, and p-values of variables thought to influence breast cancer clinical trial participation (N=358).

	Standardized total effects (standard error)	**p-value**	**Standardized direct effects**	**p-value**	**Standardized indirect effects (standard error)**	**p-value**
Mid-level of annual household income —> ever participated in a breast cancer clinical trial	0.0815 (0.0619)	0.1884	0.0815 (0.0619)	0.1884		
Employed —> mid-level annual household income	0.5254 (0.0631)	<0.0001	0.5254 (0.0631)	<0.0001		
Employed —> ever participated in a breast cancer clinical trial	0.1194 (0.0788)	0.0869	0.0766 (0.0853)	0.369	0.0428 (0.0330)	0.1945
Retired/disabled —> mid-level annual household income	0.1429 (0.0662)	0.0309	0.1429 (0.0662)	0.0309		
Retired/disabled —> ever participated in a breast cancer clinical trial	0.1209 (0.0796)	0.1290	0.1092 (0.0800)	0.1720	0.0116 (0.0104)	0.2617
Years of education —> mid-level annual household income	0.2637 (0.0446)	<0.0001	0.2637 (0.0446)	<0.0001		
Years of education —> ever participated in a breast cancer clinical trial	0.0918 (0.0536)	0.0869	0.0559 (0.575)	0.3314	0.0360 (0.0215)	0.095

Years of education —> knowledge of clinical trials score	0.2475 (0.0497)	<0.0001	0.2475 (0.0497)	<0.0001		
Years of education —> Attitudes Toward Cancer Trials Scale	0.0380 (0.0150)	0.0113			0.0380 (0.0150)	0.0113
Attitudes Toward Cancer Trials Scale —> ever participated in a breast cancer clinical trial	0.1280 (0.0519)	0.0136	0.1280 (0.0519)	0.0136		
Knowledge of clinical trials score —> Attitudes Toward Cancer Trials Scale	0.1537 (0.0517)	0.0029	0.1537 (0.0517)	0.0029		
Knowledge of clinical trials score —> ever participated in a breast cancer clinical trial	0.0585 (0.0536)	0.2753	0.0388 (0.0539)	0.4709	0.0197 (0.0104)	0.0586
Early stage breast cancer —> ever participated in a breast cancer clinical trial	-0.0932 (0.0568)	0.1010	-0.0932 (0.0568)	0.1010		

Clinical trial knowledge score ranges from 0-7 with higher scores indicating more knowledge about clinical trials. Knowledge scores equal to or greater than 5 were considered high knowledge, as this would be considered a passing grade. Attitudes Toward Cancer Trials Scale ranges from 18-126 with higher scores indicating more positive attitudes toward clinical trials. Personal beliefs and trust in the research process subscales range from 4-28; personal barriers and safety and personal and social value subscales range from 5-35.

Table 3. Model-estimated odds ratios and 95% confidence intervals assessing the association between both attitudes toward clinical trials and knowledge about clinical trials and participation in a clinical trial (N=358).

	Odds ratios (95% CI)
Respondents with high knowledge	
Positive-leaning attitudes	4.05 (0.50-32.99)
Negative-leaning attitudes	Reference
Respondents with low knowledge	
Positive-leaning attitudes	1.42 (0.60-3.35)
Negative-leaning attitudes	Reference
Respondents with positive-leaning attitudes	
High knowledge	1.04 (0.51-2.10)
Low knowledge	Reference
Respondents with negative-leaning attitudes	
High knowledge	0.36 (0.04-3.16)
Low knowledge	Reference

Model controlled for age at diagnosis, race (due to small numbers, categories with less than 20 individuals were grouped into a singular group for modeling purposes), ethnicity, cancer stage, education, employment, and income. Clinical trial knowledge score ranges from 0-7 with higher scores indicating more knowledge about clinical trials. Knowledge scores equal to or greater than 5 were considered high knowledge, as this would be considered a passing grade. Attitudes Toward Cancer Trials Scale ranges from 18-126 with higher scores indicating more positive attitudes toward clinical trials. CI=confidence intervals.

Table 4. Model-estimated odds ratios, 95% confidence intervals, and predicted probabilities exploring the association between patient-level demographics and positive-leaning attitudes toward breast cancer clinical trials (N=358).

	Odds ratios (95% CI)	**Predicted probabilities (95% CI)**
Knowledge of clinical trials		
High knowledge	1.56 (0.89-2.75)	0.81 (0.72-0.87)
Low knowledge	Reference	0.73 (0.66-0.78)
Education level		
Bachelor's degree or higher	0.72 (0.40-1.28)	0.73 (0.64-0.80)
High school diploma or lower	0.62 (0.32-1.20)	0.70 (0.57-0.80)
Some college	Reference	0.79 (0.72-0.85)
Annual household income		
$50,000 or more	1.38 (0.75-2.56)	0.79 (0.70-0.86)
Less than $50,000	Reference	0.73 (0.67-0.79)
Breast cancer stage		
Early	0.80 (0.46-1.38)	0.73 (0.66-0.80)
Late	Reference	0.78 (0.70-0.84)
Employment status		
Employed	0.69 (0.30-1.57)	0.74 (0.65-0.82)
Retired/disabled	0.71 (0.33-1.55)	0.75 (0.67-0.81)
Unemployed/other	Reference	0.81 (0.68-0.89)
Age at diagnosis		
49 year or younger	1.05 (0.62-1.77)	0.76 (0.69-0.82)
50 or older	Reference	0.75 (0.67-0.81)
Race		
Black	0.74 (0.42-1.29)	0.72 (0.62-0.80)
Other	0.71 (0.32-1.59)	0.71 (0.54-0.84)
White	Reference	0.78 (0.71-0.83)
Hispanic or Latino(a) origin or descent		
No	0.67 (0.28-1.60)	0.75 (0.69-0.79)
Yes	Reference	0.81 (0.66-0.91)

CI=confidence intervals.

Figure 1. Hypothesized conceptual model (N=358).

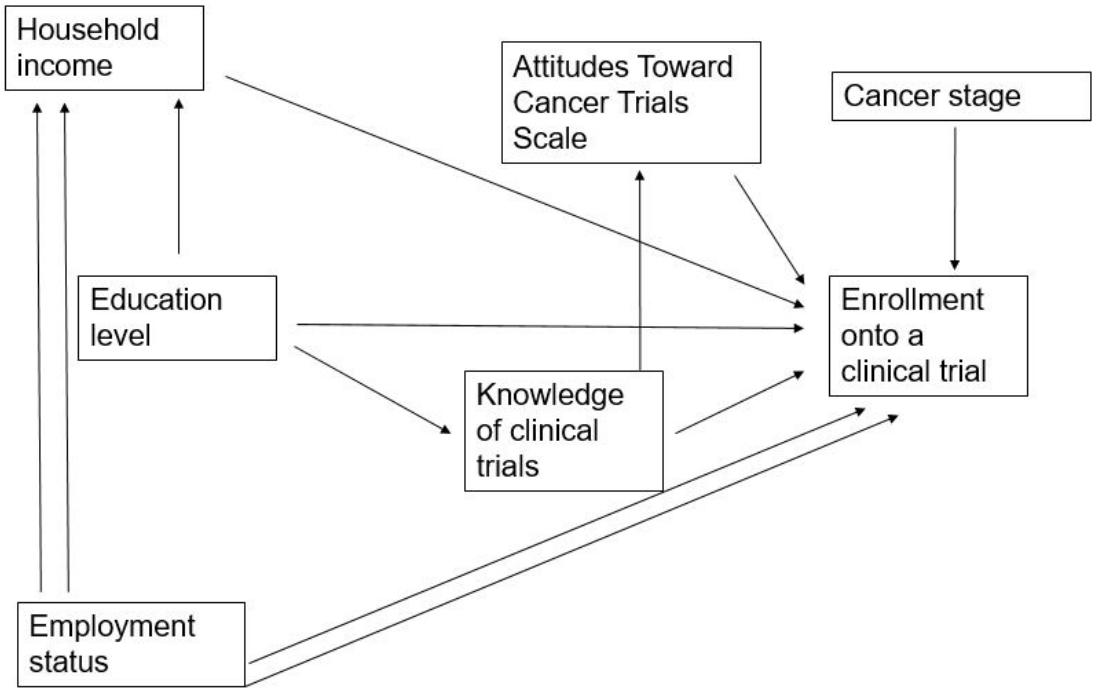
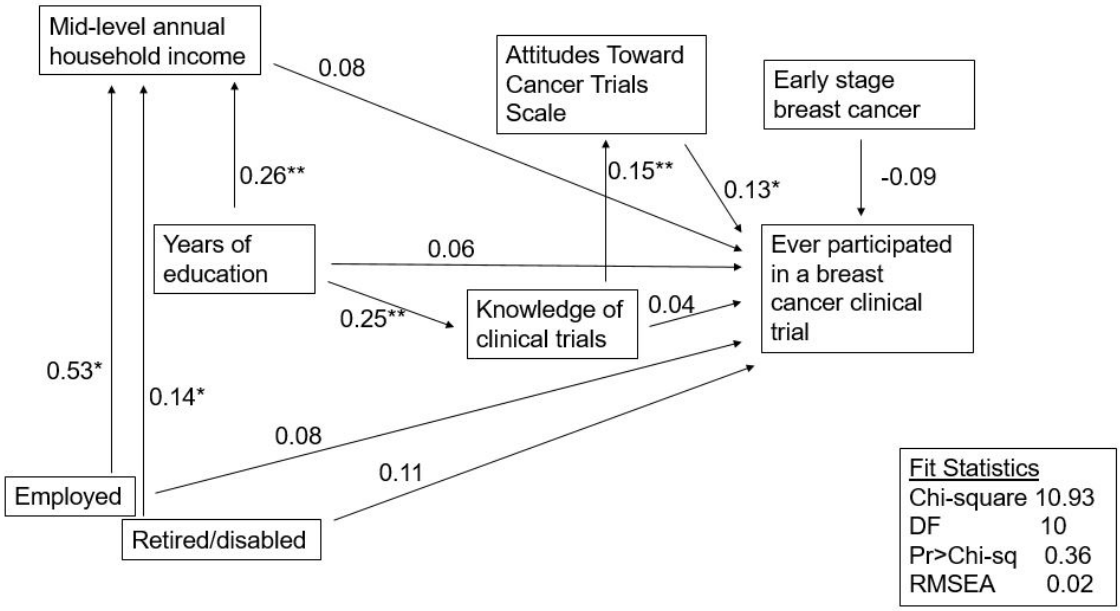
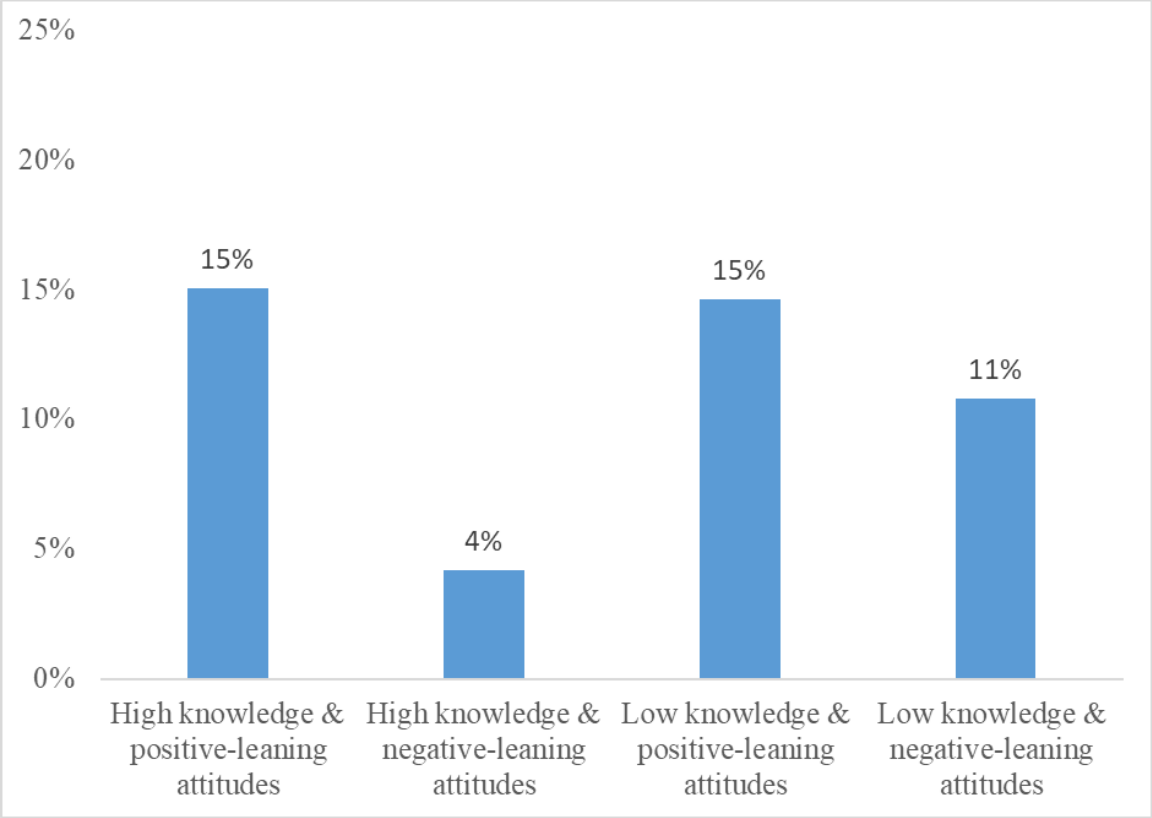


Figure 2. Final conceptual model with standardized direct effects (N=358).



Note: * p-value ≤ 0.05. ** p-value ≤ 0.01. RMSEA values less than 0.06 indicate good fit. Clinical trial knowledge score ranges from 0-7 with higher scores indicating more knowledge about clinical trials. Knowledge scores equal to or greater than 5 were considered high knowledge, as this would be considered a passing grade. Attitudes Toward Cancer Trials Scale ranges from 18-126 with higher scores indicating more positive attitudes toward clinical trials. Personal beliefs and trust in the research process subscales range from 4-28; personal barriers and safety and personal and social value subscales range from 5-35.

Figure 3. Predicted probabilities evaluating the association between both attitudes toward clinical trials and knowledge about clinical trials and participation in a clinical trial (N=358).



Model controlled for age at diagnosis, race (due to small numbers, categories with less than 20 individuals were grouped into a singular group for modeling purposes), ethnicity, cancer stage, education, employment, and income. Clinical trial knowledge score ranges from 0-7 with higher scores indicating more knowledge about clinical trials. Knowledge scores equal to or greater than 5 were considered high knowledge, as this would be considered a passing grade. Attitudes Toward Cancer Trials Scale ranges from 18-126 with higher scores indicating more positive attitudes toward clinical trials.

Supplemental Figure. Survey questions.

You are being asked to complete an online research survey from Patient Advocate Foundation. We are conducting this research because we want to learn how people feel about participating in breast cancer clinical trials.

Breast cancer clinical trials are a type of research done to learn about breast cancer and about how to improve breast cancer treatments. Your responses to this survey will build on prior research about barriers to clinical trial participation and may help breast cancer researchers improve how they conduct breast cancer clinical trials during and after the pandemic.

This survey was deemed exempt by the University of Alabama at Birmingham Institutional Review Board. Completing this survey is optional and your answers will be kept anonymous. By beginning this survey, you are providing consent to participate in this research.

This survey will take approximately 15 minutes of your time. Please mark only one answer for each question unless otherwise indicated.

Individuals who complete the entire survey will be entered into a drawing to win <u>one</u> of five digital $100 Amazon gift cards. Winners will be notified via email by Patient Advocate Foundation.

1. I agree to participate in this survey.
    - Yes
    - No

2. Have you ever been diagnosed with breast cancer?
    - Yes
    - No
3. How many years ago were you first diagnosed with breast cancer?
    - Less than 1 year ago
    - 1-5 years ago
    - 5-10 years ago
    - More than 10 years ago
4. Which of the following statements most accurately describes you?
    - I have been diagnosed with early stage breast cancer (breast cancer involving the breast with or without involving the armpit lymph glands)
    - I have been diagnosed with metastatic breast cancer (breast cancer that has spread to other parts of the body)
    - Other
5. Are you at least 18 years of age?
    - Yes
    - No
6. Have you ever participated in a breast cancer clinical trial?
    - Yes
    - No
7. Are you currently participating in a breast cancer clinical trial?
    - Yes
    - No

8. Has a breast cancer provider ever discussed a breast cancer clinical trial with you?

- Yes
- No

9. For the next questions, please mark the number indicating how much you agree or disagree with each of the statements about clinical trials:

1 = Strongly Disagree 7 = Strongly Agree	1	2	3	4	5	6	7
I'd get improved cancer treatment if I took part in a clinical trial	○	○	○	○	○	○	○
People who join clinical trials have a better chance of beating their cancer	○	○	○	○	○	○	○
Joining a clinical trial would mean I'd receive the best existing cancer treatment	○	○	○	○	○	○	○
By joining a clinical trial, I would receive better health care	○	○	○	○	○	○	○
Taking part in a clinical trial is a lot more trouble than just getting the usual treatment	○	○	○	○	○	○	○
Getting treatment in a clinical trial is less safe than getting the usual cancer treatment	○	○	○	○	○	○	○
Treatments received in a clinical trial could be unsafe for myself	○	○	○	○	○	○	○

My taking part in a clinical trial could lead to more health problems	○	○	○	○	○	○
Joining a clinical trial would make cancer treatment more difficult	○	○	○	○	○	○
In general, people should know more about clinical trials	○	○	○	○	○	○
Clinical trials are of little importance to me	○	○	○	○	○	○
Access to cancer treatment clinical trials is important to me	○	○	○	○	○	○
People who take part in clinical trials are helping all of us fight cancer	○	○	○	○	○	○
I feel certain my safety would be watched closely in a clinical trial	○	○	○	○	○	○
Doctors and nurses tell patients the truth about what to expect during a clinical trial	○	○	○	○	○	○
If I took part in a clinical, I would be treated like a guinea pig	○	○	○	○	○	○
Doctors and nurses mislead their patients who are involved in clinical trials	○	○	○	○	○	○
It would be safe for me to join a clinical trial	○	○	○	○	○	○

for treatment						
I will get my needed treatment as soon as possible if I am in a clinical trial	○	○	○	○	○	○
If I am in a clinical trial I will have to spend extra time having more tests and doctor visits	○	○	○	○	○	○
I may have to spend more time and money on transportation and childcare and may lose income due to time away from work if I participate in a clinical trial	○	○	○	○	○	○

10. Many people have not had any experience with clinical trials before. Please indicate whether you think the following statements about clinical trials are true or not.

	True (1)	False (2)	Don't know (3)
In a randomized clinical trial, the treatment you get is decided by chance	○	○	○
Clinical trials are only used when standard treatments have not worked	○	○	○
Clinical trials test treatments which nobody knows anything about	○	○	○

Randomized clinical trials are the best way to find out whether one treatment is better than another	○	○	○
Clinical trials are not appropriate for serious diseases like cancer	○	○	○
My doctor would know which treatment in a clinical trial was better	○	○	○
My doctor would make sure I got the better treatment in a clinical trial	○	○	○

11. What is your race? Check all that apply.

- American Indian/Alaska Native
- Asian
- Black/African American
- Native Hawaiian or Other Pacific Islander
- White/Caucasian
- Other

12. Are you of Hispanic or Latino(a) origin or descent?

- Yes
- No

13. Please indicate your highest level of academic achievement:

- Less than a high school diploma or equivalent
- High school diploma or equivalent
- Some college, no degree
- Associate's degree
- Bachelor's degree
- Master's or doctoral degree

14. Please indicate your current household income per year in US dollars.

- Less than $20,000
- $20,000 to $34,999
- $35,000 to $49,999
- $50,000 to $74,999
- $75,000 to $99,999
- More than $100,000

15. What is your current employment status? Please select what you consider to be your main activity.

- Working full time (≥32 hours/week)
- Working part time (1-31 hours/week)
- Unemployed, looking for work
- Unemployed, not looking for work
- In job training
- Temporarily laid off (no pay)
- Retired
- On short term disability

- On long term disability
- Permanently disabled
- I do not work
- In school
- Other

16. Please indicate your health insurance type. Pease select all that apply.

- Private (e.g. BlueCross, Cigna)
- Medicare
- Medicaid
- Tri-Care/Other Military
- Indian Health Service
- The Veterans Health Administration (VA)
- None
- Other

17. How old were you when you were first diagnosed with breast cancer?

- Under 18
- 18-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70 or older

CONCLUSION

Overall findings

My dissertation projects sought to understand multi-level reasons for underrepresentation in cancer clinical trials with a specific focus on patients who are socioeconomically vulnerable. The results of my analyses were successful in achieving my three aims.

Aim 1: Estimate associations between county-level demographics and access to NCORP and NCI-designated sites.

This cross-sectional study utilized publicly available data to map locations of both NCORP and NCI sites and used county-level demographic data from the Social Vulnerability Index and Area Health Resource Files. Overall, a very small number of individual counties have access to sites that conduct clinical trials; a total of 14% and 2% of counties have access to NCORP and NCI sites, respectively. Predominantly, NCORP and NCI sites are located in metropolitan cities. In our model results, as counties become more vulnerable, we found there was a lower likelihood of access to NCORP sites; however, there was a higher likelihood of access to NCI sites. Additionally, we found that singular counties with access to NCORP and NCI sites more often served individuals of marginalized racial and ethnic groups. However, as larger geographical areas were

considered, such as contiguous counties, there were smaller proportions of individuals of marginalized racial group with access to NCORP sites.

Aim 2: Estimate the relationship between area-level disadvantage and willingness to participate given potential systems-level changes made to breast cancer clinical trials.

This cross-sectional analysis used nationwide survey data fielded by the Patient Advocate Foundation in December 2022, a non-profit organization that offers case management and financial services to individuals with a chronic illness. We utilized modified Poisson regression models with robust standard errors to determine the association between area deprivation and willingness to participate in a future clinical trial with modifications. Overall, we found that respondents viewed the trial modifications favorably, regardless of area deprivation group: individuals living in areas of higher vs lower disadvantaged had similar likelihoods of being willing to participate for all four trial modifications. Furthermore, the systems-level changes viewed most favorably were medications being delivered to the home, ability to complete online questionnaires, and sign consent forms online.

Aim 3: Evaluate which factor (patient-level education, income, employment, knowledge, & attitudes) is the greatest contributor to participation in a breast cancer clinical trial.

This cross-sectional analysis used the same sample of individuals in Aim 2. Structural Equation Modeling was utilized to understand which factor was most strongly associated with participation in a breast cancer clinical trial within a pre-specified model for exogenous and endogenous factors influencing participation. Among the patient-level

factors, positive attitudes toward clinical trials had a modest association with clinical trial participation, while other patient-level factors did not have a statistically significant relationship with participation. Knowledge was positively associated with attitudes towards trials, even though knowledge of trials was low. When assessing the interaction between attitudes and knowledge on participation, the results of our study showed that among individuals with both high and low knowledge, individuals with positive attitudes toward cancer clinical trials had a higher likelihood of participation when compared to individuals with negative attitudes. Additionally, we explored the relationship between patient-level demographics and attitudes and found no associations.

Limitations

The results from this dissertation should be considered in light of several limitations. For the first Aim, as we used county-level data, ecological fallacies may exist. County-level findings may not be generalizable to other geographical levels nor individual-level experiences. However, we felt this was the most accurate reflection of how patients would travel across geographies to seek care. As Aims 2 and 3 used survey data from individuals seeking services from a non-profit organization, individuals in our sample may have lower financial and social resources and therefore, they may not be generalizable to the overall cancer population. For these studies, we are limited to only the individual's response and were unable to include others involved in their cancer care delivery (e.g., caregivers, providers). Finally, we cannot establish any casual inferences as these studies were exploratory in nature. For our first Aim, further information regarding when sites were included in NCORP or were designated NCI Cancer Centers is

needed. Additionally, establishing temporality between county-level demographics and access to sites would be necessary. For the second Aim, while it appears patients are in favor of modified trials, questions were regarding hypothetical participation; therefore, future research involving patients' experiences with specific modified trials is needed. Finally, regarding the third Aim, we are unable to determine if patients participated in trials due to their positive attitudes or if trial participation promoted positive attitudes toward clinical trials.

Research Implications

The results from our studies have implications at the policy and clinical levels. First, as access to healthcare is integral to cancer care, calls for an increase in community oncology sites or academic satellite hospitals to participate in NCORP could help bring clinical trial access to the most vulnerable patients. Furthermore, our results could also affect how clinical trials are conducted. As patients viewed trial modification favorably, sponsors and sites should continue to offer flexible trial modifications. Additionally, by conducting more pragmatic, decentralized, or hybrid trials there is potential to increase clinical trial participation. If trials do continue to offer modifications, future research will be needed to understand the outcomes of patients who participate in modified trials and if outcomes are similar to patients who complete non-modified trials. Furthermore, sponsors should report outcomes by social determinants of health as these data are integral to cancer outcomes and are often not captured in trials. Understanding outcomes within a trial for patients who are underrepresented in clinical trials will help researchers and clinicians understand obstacles that may arise in the real-world (i.e., when the drug is

on the market). Finally, future research is needed to understand the relationship between attitudes and clinical trial participation as targeted interventions focusing on improving attitudes toward clinical trials could increase participation in cancer clinical trials.

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APPENDIX

IRB FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration
Building 701 20th
Street South
Birmingham, AL
35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

NHSR DETERMINATION

TO: Caston, Nicole

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 28-Nov-2022

RE: IRB-300010015
Understanding how multi-level factors influence cancer clinical trial enrollment decisions by patients living in higher disadvantaged areas

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The Office of the IRB has reviewed your Application for Not Human Subjects Research Designation for the above referenced project.

The reviewer has determined this project is not subject to FDA regulations and is not Human Subjects Research. Note that any changes to the project should be resubmitted to the Office of the IRB for determination.

If you have questions or concerns, please contact the Office of the IRB at 205-934-3789.

Additional Comments: De-identified data from Patient Advocate Foundation only.

Linked Records: 000524298

University Contracts, MTA, DUA, or Subcontract/Subaward Identifier(s): 000524298