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Leveraging system sciences methods in clinical trial evaluation: An example concerning African American women diagnosed with breast cancer via the Patient Navigation in Medically Underserved Areas study

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ABSTRACT

Background: Systems science methodologies offer a promising assessment approach for clinical trials by: 1) providing an *in-silico* laboratory to conduct investigations where purely empirical research may be infeasible or unethical; and, 2) offering a more precise measurement of intervention benefits across individual, network, and population levels. We propose to assess the potential of systems sciences methodologies by quantifying the spillover effects of randomized controlled trial via empirical social network analysis and agent-based models (ABM).

Design/methods: We will evaluate the effects of the Patient Navigation in Medically Underserved Areas (PNMUA) study on adult African American participants diagnosed with breast cancer and their networks through social network analysis and agent-based modeling. First, we will survey 100 original trial participants (50 navigated, 50 non-navigated) and 150 of members of their social networks (75 from navigated, 75 non-navigated) to assess if navigation results in: 1) greater dissemination of breast health information and breast healthcare utilization throughout the trial participants' networks; and, 2) lower incremental costs, when incorporating navigation effects on trial participants *and* network members. Second, we will compare cost-effectiveness models, using a provider perspective, incorporating effects on trial participants versus trial participants and network members. Third, we will develop an ABM platform, parameterized using published data sources and PNMUA data, to examine if navigation increases the proportion of early stage breast cancer diagnoses.

Discussion: Our study results will provide promising venues for leveraging systems science methodologies in clinical trial evaluation.

1. Introduction

Breast cancer is the most common type of cancer diagnosis and leading cause of cancer death among women [1–3]. Simultaneously, African American women suffer a disproportionate burden, wherein: 1) breast cancer incidence rates are increasing and now comparable to non-Latino whites (NLWs [4] and, 2) they are approximately more likely to die from breast cancer relative to NLWs [5–8]. Patient navigation – an intervention that addresses barriers to care by individualized assistance to patients [9–13] – has been tested by clinical trials and has been increasingly implemented in public health practice and policy [14,15]. Little is known about *if* and *how* this widespread implementation will result in breast health equity at the population level [16,17]. To optimize the promise of clinical trials testing patient navigation, there is a need to use analytic approaches that 1) provide an *in-silico* laboratory to conduct investigations where purely empirical

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research may be infeasible or unethical; and, 2) offer a more precise measurement of intervention benefits across individual, network, and population levels [18–32].

Our study will address multiple gaps in the literature. First, individual-level interventions are theorized to impact participants' networks and communities [33]. Patient navigation may, for example, lead to population shifts in early stage detection by empowering AA breast cancer patients to change their communities' knowledge and behavior. Yet, these network and community spillover effects are often not assessed [33–37]. Empirical social network analysis (SNA) is an excellent tool to capture these spillover effects [27,28]. Second, few studies have characterized incremental costs associated with these spillover effects [34,38]. There is a need to consider different healthcare investments through comparing scenarios with direct only versus direct + indirect effects. Third, extrapolating empirical data from clinical trials to the population level is crucial for scaling up interventions and, ultimately, policy development. Agent-based models (ABMs) are increasingly applied to non-communicable diseases to identify when and how interventions can be optimized and to characterize spill-over effects [23,24]. A common concern however is the ability to translate ABM results to real-life settings [22]. Patient navigation provides a unique opportunity, in that it is already being adopted in public health practice and policy [16,17]. Thus, empirical data at the population level will be available in the near future to validate ABMs and ABMs may prove useful for refining health interventions that are being scaled up.

To address these gaps, we will examine potential incidental effects of patient navigation using the randomized clinical trial, Patient Navigation in Medically Underserved Areas (PNMUA) study. Our protocol highlights one approach to conduct post-hoc evaluation of clinical trials' effects on networks and populations. Toward that goal, we will examine differences in: 1) breast health information dissemination among 50 navigated PNMUA trial participants and 50 non-navigated patients who are 18 + years old, are African American, and were diagnosed with breast cancer during the PNMUA study; 2) breast health shared decision making (SDM), risk assessment, and screening among navigated and non-navigated participants' family and friends (network members) who are eligible for breast cancer screening (75 in each arm); 3) incremental costs associated with navigation when considering direct effects (i.e., PNMUA participants) and direct + indirect effects (i.e., PNMUA participants and network members); and, 4) use ABMs to quantify the impact of navigation on early stage at diagnosis.

2. Study design and methods

2.1. Overview of original clinical trial

Detailed descriptions of the PNMUA study have been published elsewhere [39–42]. Briefly, PNMUA was implemented in three facilities located in medically underserved areas in South Chicago. Eligibility criteria included self-reports of: 1) female gender; 2) age of > 18 years, 3) not being pregnant, and 4) not being referred from a primary care provider for a screening or diagnostic mammogram based on an abnormal clinical breast exam. During 2011–2014, eligible women who were referred to one of the three sites for a mammogram were identified and randomized to receive either standard care or navigation. We will focus the current study among participants who were diagnosed with breast cancer during the PNMUA study.

2.1.1. Navigation arm

Navigated women interacted with lay navigators throughout screening, diagnosis, and treatment. For the first contact and study enrollment, navigators attempted to call participants up to 10 times before their scheduled visit. During that phone visit, navigators described the study; obtained informed consent; administered a baseline survey; provided information about breast cancer and what to expect during specific breast cancer care visits; tested comprehension through a "teach back" method, such that participants relayed what they understood; addressed participants' unique barriers (e.g., costs, fatalism); encouraged women to develop questions and to participate actively in informed shared decision making; and, provided their contact information for future participant-initiated contacts. Navigators contacted participants two days prior to the scheduled appointment to remind participants and address any remaining barriers. At the initial appointment, all navigated women - those successfully contacted and those not successfully contacted – met with the navigator, who provided an abbreviated version of services described during the initial visit. If participants missed the appointment, the navigator attempted contact until successful to address patients' barriers and support rescheduling needs.

After the initial visit, navigators maintained longitudinal contact with navigated participants until the end of the PNMUA study. For participants who initially received normal results, navigators provided phone- and mail-based reminders for their annual screening appointments. When participants received abnormal results, navigators attempted immediate phone contact and provided services as described above throughout the diagnostic procedures. Subsequent contacts were made by mail, phone, and in-person, as preferred by the participant. Navigators maintained contact after women received their definitive diagnoses of breast cancer and provided the following services throughout women's treatment processes: provision of informational, emotional, and logistical support; supportive services for financial assistance options; assistance with scheduling appointments; and shared decision making processes regarding treatment options.

2.1.2. Control arm

Non-navigated women received opportunistic support by providers. Most of these participants were "passive controls" and did not interact with staff throughout screening, diagnostic, and treatment procedures.

2.2. Overview, conceptual framework and hypotheses of proposed study

This study will seek to leverage systems science methodologies to evaluate the PNMUA study's incidental network consequences on participants diagnosed with breast cancer and their network members. First, we will use validated social network designs to survey 100 women diagnosed with breast cancer during the PNMUA study (50 navigated PNMUA participants; 50 matched controls) and 150 women eligible for breast cancer screening within their networks (75 navigated, 75 non-navigated). Second, we will conduct cost-effectiveness analyses that respectively focus on PNMUA participants only versus PNMUA participants and their network members. Third, we will develop an ABM platform of AA women in Chicago, parameterized with published data sources and PNMUA data. We will model improved population-level breast health as an emergent property due to information transmission from breast cancer patients and to their network members.

Fig. 1 depicts our conceptual framework concerning the network consequences of patient navigation, as theorized by diffusion of innovation, social contagion, and social cognitive theories [20,25,26,43]. Navigators are crucial brokers. They coordinate care as part of the healthcare system and provide tailored support in response to patient's specific needs, usually as members of the patient's community [12,13]. Receiving this additional support has been associated with greater breast cancer knowledge, medical system trust and/or knowledge, and breast cancer-specific communication self-efficacy among navigated patients [12,40,44,45]. By effecting these changes to a greater degree than standard care, navigation is hypothesized to empower breast cancer patients to: 1) share information with individuals within their existing networks; 2) meet and engage new individuals about breast cancer; and, 3) become breast cancer leaders in their social circles.

We have four primary hypotheses. First, navigated participants (n = 50) will have shared more information frequently and to more individuals relative to non-navigated participants (n = 50). Second,

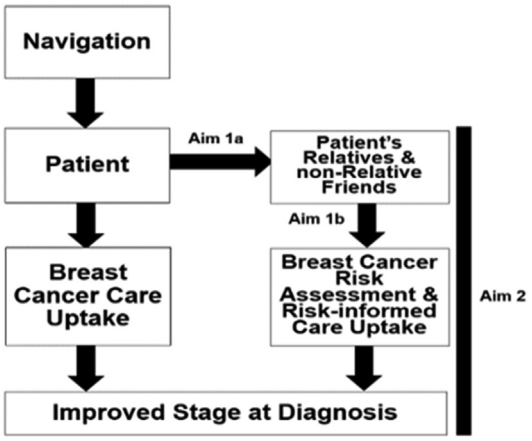

Fig. 1. Conceptual framework.

navigated women's network members (n = 75) will report greater shared decision making (SDM), risk assessment, and screening relative to non-navigated women's network members (n = 75). Third, incremental costs will be lower when incorporating the effects on navigated women's network members into cost-effectiveness analyses compared to the effects solely on navigated women. Fourth, relative to a scenario with no navigation, there will be a greater proportion of early stage breast cancer diagnoses when navigated breast cancer participants: 1) share information frequently and with many individuals within their pre-diagnosis network; 2) meet more individuals and communicate about breast cancer; and, 3) assume a more focal position in their networks [27,28,46].

2.3. Setting

This study will focus on one of the three hospitals wherein PNMUA was originally implemented in the South Side of Chicago. We selected this hospital (Hospital A), as it provided care to 90% of PNMUA participants who were diagnosed with breast cancer and preliminary analyses have suggested important hospital differences among PNMUA participants' healthcare and health outcomes. Similar to the other hospitals, this hospital is situated in a MUA designated area that exhibits high levels of concentrated poverty and racial segregation [47].

2.4. Staff and training

There will be three staff groups involved in the current study: staff who abstract medical records at Hospital A; interviewers who collect survey data at the University of Illinois at Chicago; and staff who participate in ABM development and refinement at the University of Chicago. Staff abstracting medical records: 1) are employed through Hospital A's research institute; and, 2) have years of experience abstracting medical records for research purposes. Prior to chart review, abstractors will be provided a brief description of the study and will be trained on the protocol regarding identifying participants and abstracting contact information. For survey data collection, selected interviewers: 1) have > 5 years of experience in clinical trial and observational research studies; and, 2) are either racially concordant to study participants or employed through Hospital A. Prior to engaging with participants, interviewers will be trained on all materials and procedures across a 3-month time period. Staff engaging in ABM development and refinement will have documented experience in ABM research and training in system sciences modeling methodologies.

2.5. Ethics committee approval

Study materials and processes will be in accordance with the Code of Ethics of the World Medical Association and have been approved by the Institutional Review Boards of the University of Illinois at Chicago (Sections 2.6-2.9), University of Chicago (Section 2.9), and Hospital A (Sections 2.6-2.7). Approved materials and processes include participant identification, randomization, informed consent, intervention activities, surveys completed during navigator-participant interactions, waivers of informed consent for re-contact, HIPAA waivers of authorization for medical record abstraction, and database management. More detailed information pertaining to informed consent and participant details are described in the context of study processes, as per Sections 2.6.2, 2.6.3, 2.7.2, and 2.7.3.

2.6. Unintended breast health information diffusion via PNMUA trial participants

2.6.1. Eligibility and participant identification

The study team will first review study records to identify navigated PNMUA participants who met the following criteria: 1) female patients, 2) age 18 or older, 3) who were not pregnant, 4) with initial referrals from a primary care provider for a screening mammography or a diagnostic mammography based on an abnormal clinical breast exam; 5) African American; and, 6) breast cancer diagnosis within PNMUA. Second, we will identify participants who were diagnosed with breast cancer at Hospital A and not navigated through PNMUA (i.e., passive controls). We will match navigated and non-navigated women by year of birth and year of diagnosis. We will strive for exact matching. If this is not possible due to non-response/refusal rates (see Section 2.6.2), we will use nearest neighbor matching techniques. Third, Hospital A medical records will be reviewed to obtain the most updated contact information for the sample of navigated and non-navigated PNMUA participants.

2.6.2. Recruitment of PNMUA participants

Pairs of navigated and non-navigated women will be recruited simultaneously. First, pairs will be mailed letters of recruitment by Hospital A, which will introduce the ancillary study and describe its relationship to PNMUA. Interested women will directly contact study staff, who will describe the study, obtain informed consent, and schedule interviews. For PNMUA participants who do not contact study participants, Hospital A staff will attempt contact by phone up to 10 times within 21–28 days of mailing recruitment letters. If contact is successful, study staff will provide similar information to the PNMUA participant as is described above.

2.6.3. Survey data collection and measures

After obtaining informed consent, staff will conduct a 45–60 min phone or in-person interview, based on participants' preferences. Participants will receive a $75 incentive; this amount is based on, informed by previous attempts to recruit Chicago-based AA breast cancer participants [48,49]. Table 1 depicts the constructs and associated validated instruments that will be used [48,50–60]. To note, all survey data will be collected and managed using Qualtrics electronic data capture tools.

2.6.4. Planned statistical analysis

We will conduct descriptive statistics (e.g., means for continuous variables; frequency distributions for ordinal and categorical variables) for variables listed in Table 1. To inform covariate selection, we will also conduct bivariate analyses (e.g., chi-square analyses; linear/logistic regressions, depending on outcome variable distribution) to assess how demographic, healthcare, breast health and psychosocial covariates differ by study arm as well as are associated with social network characteristics, and breast health communication. We will employ mixed models to assess the effect of navigation for each outcome (i.e., number of individuals to which PNMUA participants initiated exchanges; frequency to which PNMUA participants initiated

Table 1

Domain	Construct(s)	Data Source - Measures/Authors
Demographic/healthcare covariates	Age, gender identity, education, household income, household family size, insurance, regular source of care, last doctor check-up, and family history of breast cancer	Survey-9 relevant items from BRFSS[45]
Psychosocial covariates	Social desirability	Survey- 10-item modified Marlowe-Crowne[46]
	Medical mistrust	Survey-9-item Shea/Armstrong[47]
	Cultural misconceptions about breast cancer	Survey-15-item modified Ferrans[44]
Social network structural characteristics	Confidant name generator	Survey-5 relevant General Social Survey items/Burt[48]
	Name interpreter for five nominated alters (age, race/ethnicity, relative/non-relative)	
	Relationship examiner and network inter-relater for five nominated alters (e.g., communication frequency, duration of relationship, relationships between alters)	
Breast health communication	Information exchange about breast cancer initiated by patient & those initiated by alters for each of five nominated alters during first six months after Aim 1a's diagnosis	Survey-2-item Molina instrument[49–51]
	Environmental-based interviewing strategies related to information exchange for each of five nominated alters during first six months after Aim 1a's diagnosis	Survey-2-items[48]
	Current social connectedness related to breast health	Survey-11-item Berkman-Syme Social Network Index[52]
Breast health and healthcare use	Shared decision making practices	Survey - 2-item Control Preferences[53]
	Age at diagnosis, breast cancer treatment history	PNMUA medical records - age at diagnosis, type, date
	Breast cancer surveillance - physical examination, mammography history	Survey - 2 items from BRFSS[45]
	Breast cancer risk (genetic and non-genetic)	Survey-5-item Pedigree Assessment Tool[54]
	Risk assesment history	Survey-3-item Watson/Hoskins tool[55–56] Medical record, if HIPAA complete
	Breast cancer screening	Survey-2-item BRFSS[45] Medical record, if HIPAA complete

exchanges), adjusting for covariates and dependency due to navigator differences and shared network members, as needed.

2.6.5. Power analyses

We assessed the hypothesis H0: $\rho 2 \geq 0$ versus H1: $\rho 2 < 0$. Assuming $n = 100$, $\alpha = 0.05$, and $1\text{-}\beta = 0.8$, we calculated the effect size index f^2 ($=\rho^2/(1\text{-}\rho^2)$, where ρ^2 is squared multiple correlation coefficient of the variable being tested in multiple linear regression models. We used Cohen's (1988) measure of the effect size in multiple linear regression, wherein f2 values of 0.15 are considered medium and > 0.35 are considered large [61,62]. Our effect estimations suggest we will be powered to detect medium effects. These analyses were based on the limitation of being able to obtain, at maximum, 100 participants. This restriction is due to: 1) a limited sampling frame, given this is an ancillary study and its reliance on an already completed previous study with (< 200 participants) [39–42]; and, 2) estimates regarding willingness to participate among this specific population of African American breast cancer survivors [63]. The respective effect size indices if there were 1, 3, 5, and 7 covariates in the model are 0.083, 0.085, 0.087, and 0.089, respectively. These estimates are conservative, as they consider a scenario wherein matching is not possible.

2.6.6. Missingness and sensitivity analyses

With regard to the potential for missingness, we plan to use Full Information Maximum Likelihood procedures [57] and will conduct sensitivity analyses with available empirical data. Other sensitivity analyses will concern process data (e.g., timing of recruitment; survey mode of administration). To address our analysis of multiple outcomes, we will use the Benjamini-Hochberg (BH) false discovery rate (FDR), which limit the number of false discoveries that can occur. We will organize p-values in descending order and adjust them ($p \times I\, i = p\,(m/m+1\text{-}i)$), wherein p is the p-value, m is the number of tests, and i is the order of the particular p-value [64,65].

2.7. Unintended breast healthcare utilization of PNMUA participants' network

2.7.1. Participant identification

We are interested in how patient-driven diffusion impacts breast cancer care among screening eligible women in participants' networks. Thus, we will focus on female participants who are eligible for breast cancer screening. Based on previous social network studies with the priority population [66], we anticipate that approximately: 1) 90% of participants will be interested in recruiting network members; 2) 70% of PNMUA participants will have ≥ 1 screening eligible female as one of their originally nominated 5 network members; 3) 90% of those egos will recruit ≤ 3 screening-eligible women to participate; and, 4) among those screening-eligible women, approximately 96% will identify as AA and 56% will be relatives of the ego participant.

With regard to process, interviewers will first identify potential participants when administering questionnaires to PNMUA participants. When collecting network data, staff will be identifying network members who are eligible for breast cancer screening (i.e., 50–74 year old women according to US Preventive Services Task Force [67]).

2.7.2. Recruitment of PNMUA participants' network members

If PNMUA participants identify network members who are eligible for breast cancer screening, staff will ask them if they would be interested in recruiting these network members for subsequent interviews. Interested PNMUA participants will receive a script to recruit their network members verbally and recruitment brochures. Study staff will also record the information of network members (first names, first letter of last name) that each PNMUA participant indicates they will recruit. Interested network members will contact study staff by phone, provide study staff with the information of the PNMUA participant (first name, first letter of last name) who referred them, receive a brief description of the study, and undergo screening and consent. Eligibility criteria for network members are: 1) eligible for breast cancer screening according to the US Preventive Services Task Force [67]; and, 2) a nominated network member from a PNMUA participant.

At the end of the study, staff will contact PNMUA participants who agreed to invite participants to ask about their recruitment efforts. If they self-report that they invited network members, PNMUA participants will receive $25. This incentive will be given regardless of whether network members contact staff or not.

2.7.3. Survey data collection and measures

Section 2.6.3 lists the procedures for informed consent and data

collection. Table 1 also depicts the constructs, associated aims, and validated instruments that will be used. To note, all survey data will be collected and managed using Qualtrics electronic data capture tools [48,50–60,68]. Staff will conduct a 45–60 min phone or in-person survey, based on participants' preferences. For participants who agree to complete HIPAA and release their medical record information for the teams, medical record chart data will be abstracted. Participants who don't complete HIPAA Authorization or do not allow access to their MRs will remain eligible to participate in surveys.

2.7.4. Planned statistical analysis

To inform covariate selection, we will also conduct bivariate analyses (e.g., chi-square analyses; linear/logistic regressions, depending on outcome variable distribution) to assess how demographic, healthcare, and psychosocial covariates differ by study arm as well as are associated with social network characteristics, and breast health behaviors. We will employ exponential random graph models [69], that incorporate the number of individuals in multiple networks and the number of networks per individual. This model provides a statistically robust solution for interdependence-oriented graphs. Parameters will be estimated using maximum pseudo-likelihood estimation. The influence of PNMUA participants' navigation on outcomes (i.e., network members' shared decision making practices, risk assessment history, and breast cancer screening) will be determined using conditional likelihood ratio statistics from two nested models (with and without navigation) and a series of nested models with potential confounders, including navigator identity, as in previous studies [70]. We calculated the minimum detectable effect size (MDES) for generalized linear mixed models with random intercepts, assuming $n = 100$, $\alpha = 0.05$, $1\text{-}\beta = 0.8$, an intracluster correlation coefficient of 0.05, an equal allocation of clusters between the two groups ($n1 = n2 = 35$) and an equal cluster size (m).

2.7.5. Power analyses

We calculated effect sizes (p2) that can be detected with $\alpha = 0.05$, $1\text{-}\beta = 0.8$, noting the sample size of 150 (75 family and friends overall for 50 navigated patients; 75 per 50 family and friends overall for 50 non-navigated patients) and assuming that the cluster size is 2 or 3 and proportion of outcome uptake in the control group (p1) is 0.2 or 0.5, respectively. When assuming a p1 of 0.02, the proportion of breast healthcare utilization for cluster sizes of 2 and 3 were respectively 0.42 and 0.38. When assuming a p1 of 0.5, the proportion of breast healthcare utilization for cluster sizes of 2 and 3 were respectively 0.73 and 0.69.

2.7.6. Missingness, multiple outcomes and sensitivity analyses

Procedures to address missingness, multiple outcomes, and sensitivity analyses are described in 2.6.6.

2.8. Including PNMUA network effects in cost-effectiveness analyses

2.8.1. Cost data

Patient navigation costs will be abstracted from hospital invoices. Specifically, 60% of total direct costs related to coverage of navigator time will be used as an estimate of workforce coverage needed to run the program [17,71]. The other 40% of costs will be considered to be related to training, conducting surveys and other research related activities. Overhead costs (office space, equipment, etc) related to the navigators will be estimated to be 49% of the direct costs based on the invoices from the program. These cost estimates will be used to estimate the total incremental cost of running the program and combined with counts of participants to estimate the average costs of navigation per participant. It is assumed that no additional costs is incurred for alter outreach, as network members will be recruited through referrals and not navigated.

2.8.2. Effect data

The probability of screening adherence will be taken from data reported in Table 1 for PNMUA participants and network members. Subsequently, these data will be entered in a spreadsheet model that has been based on published evidence-based models [72–76]. Fundamentally, the projections depend on the difference in probability of screening adherence between navigated and non-navigated patients and network members, rates of breast cancer, and projections of quality adjusted life years (QALY) associated with screening rates.

2.8.3. Planned cost effectiveness analysis

Two incremental cost-effectiveness ratios will be calculated that respectively measure the costs of navigation and the direct effects of navigation (PNMUA participants) and the costs of navigation with the combination of direct and indirect effects (PNMUA participants and network members). The impact of model inputs will be assessed in sensitivity analyses, using ranges from study records, published literature [10,64] and the Bureau of Labor Statistics [77].

2.9. Modeling population effects of PNMUA across 20 years

2.9.1. Overview

The primary set of outcomes our ABM seeks to inform concerns the impact of patient navigation on stage at diagnosis at the population level. Given this, our synthetic ABM will consist of at least two counterfactual scenarios (i.e., one control and one experimental scenario which will include navigation). The control setting will include standard care with no patient navigation. The experimental setting will include patient navigation as it is currently practiced in Hospital A and other Chicago-based hospitals. The specific population for which this model applies concerns screening-eligible AA women. The main outcome, noted above, is stage of diagnosis at the population-level. We will further attempt to complement our findings by computing R0, wherein we calculate the difference in "reproductive rate" of the spread of information about breast cancer care between the control and navigated scenarios [78,79], to complement our findings. Secondarily, our ABM will allow us to consider more granular outcomes, including: 1) the impact of symptomatic status at screening; 2) the impacts of different network mechanisms (e.g., changes in communication, network size, network position) on AA population-level stage at diagnosis; and, 3) the effects of navigating women with higher genetic breast cancer risk.

2.9.2. Data sources

Published literature, public data, and proprietary data from our team and Advisory Board will inform ranges for inputs. Demographic, healthcare access, and spatial distribution characteristics for AA women will be drawn from the US Census and other public databases [80–83]. Social network characteristics and communication patterns for AA women will be drawn from BCCC's ancillary cross-sectional social network study [66] and other published literature on social networks of AA breast cancer patients [84,85] and other age-, race-, and geographically similar populations (e.g., the National Social Life, Health, and Aging. project) [86–88]. For breast cancer care uptake of initially non-affected members of the network, we will use BRFSS data with regard to receipt of breast cancer screening among AAs [50]. With regard to navigation, we will use the Metropolitan Chicago Breast Cancer Task Force's data and published literature on the distribution of facilities that provide navigation [8], and navigation effects on cancer care uptake and stage at diagnosis [12,13,89]. Based on current practices, women are assumed to be navigated until they complete care (e.g., diagnostic follow-up; treatment). For breast cancer, we will use data from published literature for AAs' prevalence of breast cancer risk factors [90,91], breast cancer transition probabilities [92], rates of false-positives and false-negatives [92–95], linkages between screening and stage at diagnosis [49,96,97], NCI's Surveillance Epidemiology and Ends Results (SEER) data for AAs' cancer incidence, stage at diagnosis, and survival data

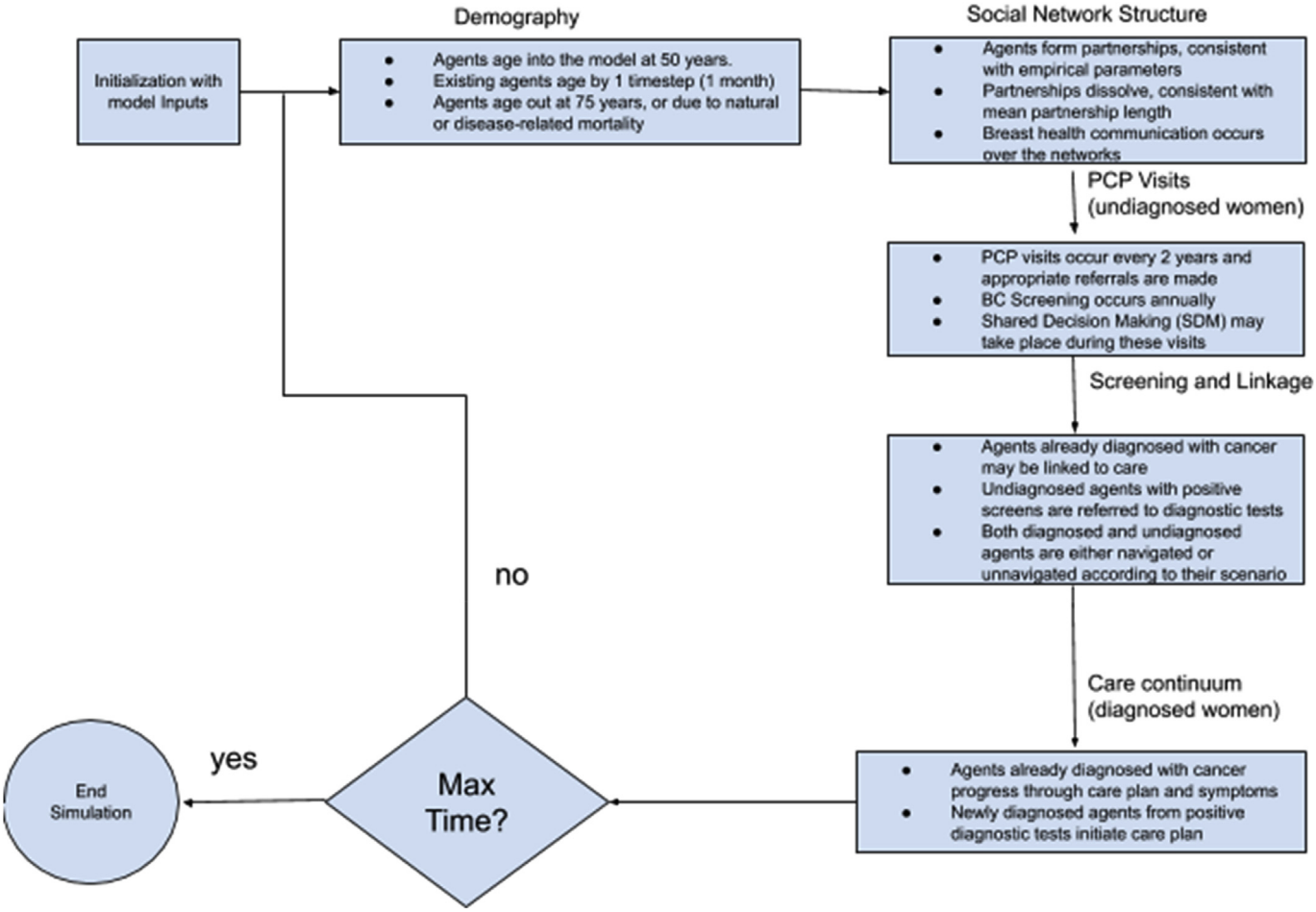

Fig. 2. Flowchart depicting the various steps that occur in the model. ("PCP" is primary care provider).

[98].

2.9.3. Participants and measures

Each scenario will consist of 1000 AA breast cancer patients. In the base scenario, no individual will receive navigation. In the navigation scenario, all women who receive a PCP referral for screening or diagnostic care will be navigated. These patients' models will include up to 10 network members total. We will have two synthetic populations that cumulatively contain a maximum of 10,000 individuals. Each individual will have a set of socio-demographic attributes (e.g., age, neighborhood), biological attributes (e.g., symptom severity; breast cancer subtype (hormone+, hormone-); risk factors (e.g., age, BMI > 30, menopausal status, number of first degree relatives with breast cancer) and breast cancer care behaviors (e.g., PCP visits, screening, diagnostic care). Aging, screening, incidence, disease progression (e.g., presence of symptoms), and breast cancer care behaviors among initially undiagnosed relatives and non-relatives will occur at each temporal step, informed by published literature and SEER data (see Section 2.9.2). Breast cancer care behaviors (days to appointments) and recommended referrals (screening versus diagnostic care) will be dependent on symptom severity and behaviors from the previous temporal step (e.g., decision to not visit PCP). Network parameters to be included are: mean relationship duration, the mean number of ego-alter relationships, the "degree distribution (i.e., number of nodes that report 0, 1,2…relationships), and mixing criteria (e.g., mean number of partnerships between first degree relatives). The model will incorporate communication feedback loops, including network-based parameters that capture mixing based on age, and residential neighborhood-based mixing, and cross-sectional (momentary) distribution of the number of these relationships at any time. Populations will evolve over time, in such a way that the empirical network structures are maintained within statistical variation of the parameters, as has been shown in a number of network modeling studies [99–101].

2.9.4. ABM development

We will develop the ABM using the iterative process outlined by North and Macal [102], in incremental stages that incorporate study team/Advisory Board feedback at each stage. Our model will be calibrated to data sources described in section 3.6.1. We will use the "statnet" suite [103,104], which provides separable temporal exponential random graph models (STERGMs), a statistically robust framework to model to simulate dynamic networks over long time frames [105,106].

We will define a number of parameters related to breast cancer progression, biological factors, social behavior and network structure in this population (sources in Section 2.9.2). The core model expresses the probability of tie formation at a given time, constrained by parameters specified by the user. In a logit-transformed form, this formation model is $logit\,(p(y_{ij,t} = 1|Y^c_{ij,t-1}, y_{ij,t-1} = 0)) = \delta\theta\eta(\boldsymbol{m}_1, \ldots, \boldsymbol{m}_p)$, where $y_{ij,t}$(i.e. the value of the dyad at time t), that has the value 1 if nodes i and j have a relationship at time t, and is 0 otherwise. The variable $y^c_{ij,t}$ represents the rest of the network excluding the tie information of i and j. The η-functions are a set of statistics $\boldsymbol{m}_1, \ldots, \boldsymbol{m}_p$ (estimated from empirical data) that we will specify to match the modeled network structure with empirical network structure, the vector θ represents the coefficients of these statistics, and the δ functions are "change statistics," defined as the change in statistics associated with a toggle of the dyad y_{ij} from 0 to 1. The specific network statistics η that we will use are: age and

residential neighborhood -based mixing between the navigated and non-navigated patients and their network members, cross-sectional (momentary) distribution of the number of these relationships at any time. Existing relationships between patients and network members will dissolve according as per a Bernoulli model of the form $logit\,(p(y_{ij,t} = 1|Y^{c}_{ij,t-1})) = \theta_{diss}$, where θ_{diss} is the coefficient associated with the dissolution of one tie (which corresponds to a change statistic of 1, in absolute value).

This setup provides the synthetics agents and their networks on which processes of navigation, communication and subsequent screening are simulated. We will consider various scenarios, including different network mechanisms (e.g., greater communication between patient and pre-diagnosis network members, increases in network size, changes in network position) and where navigation is only delivered to patients with high genetic risk. We will examine how these behavioral patterns result in improved stage at diagnosis at the population level. Simulations will be repeated for statistical robustness; the number of repetitions is determined adaptively [107]. The various steps in the operation of the ABM are illustrated in the flow diagram provided in Fig. 2 below.

2.9.5. Model validation

Model validation [108–114] consists of systematically comparing simulation model results to data obtained from real world systems. We will first create a baseline model for the explicit purpose of calibration. During the validation step, the model will be run for a range of input parameters, including: (1) vital population dynamics (e.g. rates of entry and exit of agents into and from the model, population age structure); (2) social network structure (e.g., mean relationship duration, the mean number of ego-alter relationships, the “degree distribution, mixing criteria (e.g., mean number of partnerships between first degree relatives); (2) disease progression (e.g. rates of development of hormone-positive and hormone-negative cancers, corresponding to the rates of various risk factors, including genetic risk and obesity), and, (3) clinical engagement (e.g. rates of diagnostic referrals and diagnoses). Multiple simulations will be run to account for the measurement uncertainty of each of these parameters. Input parameters, including the social network structure, demographic parameters like age structure, communication variables such as strength and frequency of communication, will be monitored to ensure that their simulated values are within statistical variation of the target values. Examining effects of changes in inputs will help us develop a well-calibrated model, with a quantified uncertainty assessment. Sensitivity analyses will incorporate a range of synthetic population sizes (n = 500 to 10,000) to enable examination of uncertainty related to scaling. With the input parameters thus calibrated, we will experiment with various schemes of patient navigation and measure the impact on stage of diagnosis at the population level.

2.10. Study management

The Principal Investigators (PIs) across the different sites (Molina (UIC), Khanna (UofC), Watson (UIC), Villines (Advocate)) are responsible for protocol development and implementation and dissemination of study findings in manuscripts and conference presentations. The PIs will communicate on a weekly basis to discuss study progress. Further, Dr. Watson will establish an advisory board composed of scientific leaders and community partners with expertise in patient navigation, breast cancer, and disparities in Chicago. This advisory will meet with Drs. Watson and Molina on a quarterly basis to discuss study design, progress, and results. With regard to empirical social network analysis and cost-effectiveness analyses, Dr. Molina and Mrs. Villines will oversee data collection and quality assurance (i.e., study logs; surveys) through weekly staff meetings. First, Mrs. Villines will oversee chart review processes, including meeting with the team of medical record abstractors and reviewing study documents. Second, Dr. Molina will ensure activities are handled according to survey protocols by meeting with interviewers and checking study logs on a weekly basis (i.e., If successful contact was noted, was consent obtained? Were surveys completed?). Third, Dr. Molina will lead abstraction of cost data. Staff at the University of Illinois at Chicago will develop and manage a complete study database that leverages diverse data sources (i.e., medical records; publicly available ecological data; survey data in Table 1; cost data) and Dr. Molina will oversee database management via bimonthly meetings with data entry and biostatistician staff. With regard to confidentiality, patients' names will not be included in datasets. All patients will be assigned a unique study number. All data will be stored on password protected, encrypted network drives. Paper copies of consent forms and questionnaires will be stored in a locked cabinet in Dr. Molina's locked office. With regard to ABM platforms, Drs. Khanna and Molina will oversee model development and refinement processes. The ABM platforms will be housed at the University of Chicago.

3. Discussion

Patient navigation is a promising strategy to eliminate disparities throughout the breast cancer care continuum. Our study offers important contributions to intervention science. First, capturing network effects from individual-level interventions will optimize our ability to choose between effective individual, network, and other multi-level approaches. Our project will provide a template for a new approach to intervention science, wherein *all* programs (i.e., not just network and multilevel programs) examine effects at multiple levels to enable an accurate comparison of individual-level and other types of approaches [28]. Second, incorporating network data in cost-effectiveness analyses is innovative for considering different healthcare investments. Few studies have characterized incremental costs associated with diffusion of information and behavior change [34,38]. To our knowledge, no studies have incorporated incidental network effects of individual-level interventions into cost analyses. Third, expanding the use of agent-based modeling to examine network and biological factors in non-communicable diseases is critical for associated program planning. Our design allows us to model network mechanisms that can generate population effects, which can detail how future network-based navigation trials should be planned. Our inclusion of biological factors for a non-communicable disease is novel [24] and timely for refining navigation processes in the era of precision medicine (e.g., targeting high-risk individuals; training survivors to advise others based on individualized risk information) [115,116].

4. Limitations

We acknowledge several limitations to this study. This study draws from a clinical trial that used non-probability recruitment strategies. Relatedly, attrition and associated non-response is expected, given this ancillary study will occur several years after the original study. Further, while we have sought to address differences in navigation by incorporating navigator identity in our models, likely there may be residual effects. Given this, our findings are not likely to be generalizable. Matching may not be possible due to differential non-response between navigated and non-navigated women, resulting in selection bias. Further, our study is limited by a small sample size due to its design as a ‘secondary analysis’ of a larger study that has already been completed and estimated attrition/willingness to participate rates. Our survey design, based on egocentric metrics, is due to recall and social desirability bias. With regard to network members, we focus on a subset of members from PNMUA participants' social networks. We focus on them, as they are most likely to be impacted by breast cancer; yet, breast cancer can occur among younger and older women as well as among men. Our sample variation may be reduced, if only a portion of PNMUA participants recruit network members. Survey data will only be available for network members who do not complete HIPAA forms.

Limitations regarding cost-effectiveness analyses include relying on self-report data for indirect effects, limited power to assess indirect effects due to the relatively short time-frame, and not using the societal perspective. Tracking costs for a societal perspective would require data collection beyond the scope of this study. Limitations include the outcomes' dependence on input parameter data. Regarding the ABM, issues may emerge as the collection of empirical data proceeds and comparisons occur regarding navigation's impact on stage at diagnosis between ABM outputs at the population level and empirical data at the network level. Another limitation concerns uncertainty associated with scaling.

5. Conclusion

In conclusion, our results will provide crucial information about the effectiveness of patient navigation at network and population levels. Our design provides a protocol for incorporating system sciences methods to evaluate diverse health equity intervention approaches that are already being implemented in public health practice and policy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2019.100411.

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