PORTAL: Patient-reported Outcomes after Routine Treatment of Atypical Lesions

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1.0 INTRODUCTION

1.1 Overview

Ductal Carcinoma in Situ (DCIS): A disease of screening with potential risks and burdens

DCIS was rarely diagnosed prior to widespread use of mammography. Although mammography has been shown to reduce overall breast cancer mortality by over 20%,[1] there is growing concern that for some patients, particularly those with DCIS, breast cancer screening may unintentionally cause harm by introducing additional procedures, promoting anxiety, and detecting cancers that may never cause illness. Advances in epidemiology and cancer biology have shown that the group of diseases currently deemed "cancers" are actually many conditions with enormous variation in biologic behavior, and that screening uncovers some conditions that may never impact a person's overall health if left undetected.[2-6] The term "**overdiagnosis**" has been used to define these conditions including DCIS, that look like early cancer, but are not destined to cause symptoms or death during a patient's lifetime.[7] Attempts to resolve the controversy that has grown around the best management of these overdiagnosed conditions, including calls to remove the word "cancer" from their description,[8,9] have garnered intense interest, anxiety, and scrutiny from patients, their families, and other healthcare stakeholders.

There is a general consensus that much of this burden derives from the treatment of DCIS. Currently, almost all DCIS is treated aggressively according to guideline-concordant care (GCC); of those treated, the majority may not benefit if they would not have developed cancer. An alternative to GCC is active surveillance (AS). Currently, only 3% of women in the United States with DCIS opt for AS (if given the choice). However, in order to consider AS as a future treatment option for DCIS, it is imperative that long-term health and quality of life (QOL) outcomes resulting from AS are critically evaluated.

The overarching goal for this study is to evaluate the benefits and harms of currently accepted GCC for DCIS compared to an AS strategy using cross-sectional patient survey data. The primary outcomes will be diagnosis of cancer and severity of chronic pain. The study will also provide rigorous comparative evidence regarding other outcomes of importance to patients including treatment-free survival, quality of life, anxiety, fear of another breast event such as DCIS or invasive breast cancer (IBC) in the affected breast/chest wall, or more rarely, elsewhere in the body (a.k.a recurrence), or a new primary breast cancer in the other breast. Additionally, body image associated with AS will be compared to that of GCC to further evaluate the benefits and harms of treatment versus AS for DCIS.

It is anticipated that the study will significantly facilitate the understanding of DCIS, its treatments, and outcomes of those treatments, which will benefit future patients. Therefore, the societal benefit could be substantial.

1.2 Background and rationale

Annually, approximately 65 million women undergo mammographic screening in the United States at a cost of over 13 billion dollars. Almost one in 1300 mammograms (.08%) will detect ductal carcinoma *in situ*, or DCIS,[10] traditionally considered the earliest detectable form of breast cancer. Over 62,000 women in the United States will be diagnosed with noninvasive breast cancer this year alone (87% of which is DCIS, totaling over 53,000 cases per year). Almost all of these diagnoses are made in completely asymptomatic individuals.[5] DCIS is characterized by a proliferation of malignant cells confined to the milk ducts of the breast.[11] Unlike invasive cancer, DCIS cells remain trapped within the breast duct and therefore have little potential to spread to distant organ sites and cause symptoms or death. Without treatment, it is estimated that only 20-30% of DCIS will progress to invasive cancer.[12,13] However, once diagnosed, over 97% of women are treated according to current guidelines with a combination of surgery, radiation and hormonal therapy treatments similar to those recommended to patients with invasive breast cancer. This is different than treatments for other breast conditions, such as atypical ductal hyperplasia (ADH) or lobular carcinoma in situ (LCIS), which are also known to confer an increased risk of breast cancer.

Impact of DCIS on the health of individuals and populations.

Overdiagnosis and overtreatment resulting from mammographic screening have been reported to be as high as 1 in 4 patients (25%) diagnosed with breast cancer,[14-17] although the absence of standard definitions for measuring overdiagnosis has led to much uncertainty around this estimate.[18] The national health care expenditure resulting from false positive mammograms and breast cancer overdiagnosis has been estimated to approach $4 billion annually.[19] There is general consensus that much of this burden derives from the treatment of DCIS; for those estimated 40,000 women per year whose DCIS may never have progressed even without treatment, medical intervention can only harm. In those women who undergo surgical management of DCIS, there is risk of developing a number of short and long-term adverse events and side effects ranging from complications of anesthesia and loss of work due to treatment, to cosmetic changes and persistent pain at the surgical site. Importantly, pain after lumpectomy may be as prevalent as that after total mastectomy with estimates ranging from 25-60%.[20-22] Persistent postsurgical pain is rated by patients as the most troubling symptom,[23] leading to disability and psychological distress, and is often resistant to management;[24] notably, much of these data have been collected in women with cancer, not DCIS.[25]

Atypical ductal hyperplasia (ADH) is a model of active surveillance for breast conditions.

Since over 97% of women receive treatment for their disease immediately upon diagnosis, it has been difficult to evaluate the outcomes of an AS strategy for DCIS.[26] However, there are other analogous clinical scenarios in which women are identified to be at increased risk for breast cancer, and are routinely offered close surveillance. One such example is atypical ductal hyperplasia (ADH) which, much like DCIS, is often diagnosed on a biopsy performed for a mammographic abnormality. ADH is found in approximately 10% of all benign breast biopsies, and is associated with the highest future risk of breast cancer among all benign diagnoses.[27] It shares many histologic features with low grade DCIS for which it is often mistaken, even by specialized breast pathologists.[28] The lifetime cumulative risk of invasive cancer among women with ADH has been reported to approach 15% at 25 years (Figure 1a), equivalent to approximately half the risk for invasive cancer in women not recognized to have DCIS and who were thus managed with biopsy alone (Figure 1b). [29-32] The treatment recommendation for women with ADH is not surgery or radiation but rather close or active surveillance, usually with the option of endocrine therapy such as tamoxifen to reduce risk of subsequent invasive cancer.[29]

Lobular neoplasia (LN) is another example of a risk marker for invasive breast cancer.

Lobular neoplasia is characterized by the proliferation of uniform rounded cells which arise from the terminal ductal lobular units. These cells have relatively little cytoplasm, are dis-cohesive, and may spread along the ducts in a Pagetoid fashion. If the cells occupy and distend more than 50% of the acini, the condition is termed lobular carcinoma in situ (LCIS), otherwise it is termed atypical lobular hyperplasia (ALH).[33] Although the distinction between the two conditions is one of degree, the more extensive changes seen in LCIS are associated with a higher risk of subsequent malignancy than occurs in ALH. Previous studies have suggested that LN is predominantly a condition found in pre-menopausal women. A study of women registered on the Surveillance, Epidemiology and End Results (SEER) database in the US shows a 38% increase in the incidence of what in the SEER database is termed LCIS between 2000 and 2009, from 2.0/100,000 to 2.75/100,000 in females aged 18-80.[34] Two previous studies of the SEER database[35,36] suggest that there has been a three to four-fold increase in LCIS diagnoses since 1978 (women with ALH were not included in these studies), predominantly among post-menopausal women. This increase is explained, at least in part, by the increasing use of screening mammography and the increasing proportion of women who undergo percutaneous needle biopsy in the investigation of screen-detected abnormalities, particularly microcalcifications.

A recent study of 1060 women with LCIS reported bilateral synchronous LCIS in only 2% of cases,[37] and in the same series none of the 56 women who underwent bilateral prophylactic mastectomy were reported as having bilateral LN, although six had contralateral occult cancers (three invasive carcinomas and three DCIS). Lobular neoplasia has long been regarded as a marker for an increased risk of subsequent malignancy rather than as a precursor. The known increase in breast cancer risk in both breasts has been cited as a justification for this view. However, more recently, the hypothesis has emerged that, at least in some women, LN may be a non-obligate precursor of invasive malignancy.[38] The risk of malignancy appears to be higher in LCIS than ALH, estimated to be 8-10 times and 4-5 times background incidence respectively.[39]

There is evidence for tamoxifen to reduce the risk of invasive cancer in women with LCIS by 56% in the NSABP P-1 study published in 1998[40] and raloxifene to have a similar protective effect. [41] Chemoprevention has also been shown to reduce the risk of invasive cancer in a recently published longitudinal study.[37]

Thus, we propose that the recommended management of women with ADH and LCIS or ALH is a model for what an active surveillance (AS) approach would be for DCIS including close follow-up and the option of chemoprevention.

Current gaps in evidence.

In 2009, the National Cancer Institute (NCI) convened a State-of-the-Science conference that identified the most critical research questions around DCIS, including investigations on the impact of DCIS on QOL and trials evaluating the comparative effectiveness of DCIS treatment strategies.[42] Further, the American Cancer Society and National Institutes of Health (NIH) published the summary of an NCI DCIS Workshop in 2010 that reviewed current issues in DCIS and identified risk communication as a priority area for future study.[43] However to date, data remain lacking in all of these areas.

Current treatment options routinely offered for DCIS include surgery (lumpectomy or mastectomy),

radiation (radiation or none) and hormonal therapy (Table 1). Increasingly, some women choose to undergo bilateral mastectomy.[44] These options constitute GCC according to National Comprehensive Cancer Network (NCCN) treatment recommendations.[45] Between 1991 and 2010, 23.8% of women diagnosed with DCIS in the United States underwent mastectomy, 43% lumpectomy with radiation, and 26.5% lumpectomy without radiation, based on data from the Surveillance, Epidemiology, and End Points Registry.[26] Among the 97% of women with DCIS treated with GCC, neither randomized trials or retrospective studies to date have shown a survival advantage of any treatment option over another.[26] To date, none of the treatment options has ever been compared to AS.

Table 1. Guideline concordant care (GCC) and Active surveillance (AS) options for DCIS. All treatments offered as part of published guidelines mandate surgical excision to negative margins and consideration for adjuvant radiation or endocrine therapy.

	Intent	Surgery	Radiation	Endocrine Therapy
Guideline- Concordant Care (GCC)	Treatment at time of diagnosis for all patients	lumpectomy	yes	yes
				no
			no	yes
				no
		mastectomy	no	yes
				no
Active Surveillance (AS)	Treatment only for those who progress during surveillance	none	no	no
				yes

Moreover, the impact of GCC and AS for DCIS on quality of life have not been carefully evaluated. Although research suggests that over 40% of women who are provided risk/benefit information regarding DCIS treatment would consider non-surgical management,[46] the clinical outcomes and patient reported outcomes (PRO) of active surveillance have never been studied. Thus women (and their doctors) face a tremendous burden of uncertainty when considering the tradeoffs of GCC or AS for DCIS.[47,48] This is likely compounded by the relative lack of information and heterogeneity in opinions regarding the optimal treatment of DCIS.[43,49]

Potential for study to improve health care and outcomes.

This year in the United States alone, approximately 50,000 women will undergo treatment for DCIS, of whom only 20-30% may benefit. Evidence to compare clinical outcomes and patient reported outcomes between GCC and AS is critically needed to reduce the harms and understand the trade-offs of GCC versus AS for DCIS. This project will provide clear, objective, evidence-based information for patients, health care providers and other stakeholders regarding the benefits and harms of DCIS treatment. Moreover, this project will create a path forward for mitigating the potential for overtreatment of other screen-detected conditions.

2.0 OBJECTIVES

2.1 Relationship of aims to significance of the proposed study.

The overarching goal for this study is to evaluate the benefits and harms of currently accepted GCC for DCIS compared to an active surveillance (AS) strategy using cross-sectional patient survey data. The broad, long-term objective of this project is to enable patients with DCIS, with their doctors, to make

informed decisions about their care based on the highest possible quality evidence about DCIS treatment, including those treatment options that fall outside of current GCC.

2.2 Hypothesis and Specific Aims:

We hypothesize that there are differences in patient-centered clinical outcomes and Patient Reported Outcomes (PROs) between women who choose GCC versus AS, and that these differences can be compared using advanced analytic methods to allow for the expected treatment selection biases between groups.

The specific aims of this study are the following:

Aim 1. Compare patient-reported outcomes (PROs) between patients diagnosed with ductal carcinoma in situ (DCIS) who received GCC to patients diagnosed with DCIS who underwent AS as well as those diagnosed with atypical ductal hyperplasia (ADH), and lobular carcinoma in situ LCIS/atypical lobular hyperplasia (ALH) (as proxies for DCIS active surveillance (AS) group) in a cross-sectional patient cohort at 6 selected study sites.

PROs will be collected from surveys administered to patients diagnosed for either DCIS, ADH, LCIS, or ALH between January 1, 2012 and June 30, 2017 at each of six study sites: Duke University Medical Center (DUMC), Dana-Farber Cancer Institute (DFCI), MD Anderson Cancer Center (MDACC), Massachusetts General Hospital (MGH), Newton Wellesley Hospital (NWH), and Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) in clinical affiliation with South Shore Hospital (DFCI @ SSH). We are planning for survey data collection to begin in September 2017, but will officially commence upon IRB approval at each recruiting site. MDACC received their site's IRB approval on December 6, 2017 and has now been added to the DFCI IRB as a site. MDACC will now complete applicable study procedures as outlined in this protocol. DUMC received their site's IRB approval on February 27, 2018 and has now been added to the DFCI IRB as a site. Duke will now complete study procedures as outlined in this protocol. MGH has been added to the DFCI IRB as a site. MGH will now complete study procedures as outlined in this protocol. DFCI @ SSH has been added to the DFCI IRB as a site. DFCI @ SSH will now complete study procedures as outlined in this protocol. The DFCI study team will complete all patient recruitment steps for DFCI @ SSH. NWH has been added to the DFCI IRB as a site. NWH will now complete study procedures as outlined in this protocol.

Once enrollment begins at a site, the recruitment and survey phases will take place over an 18-month period, or until we reach our enrollment goal. Medical records will be accessed through the duration of the recruitment phase, which we anticipate will be completed in 2019, to look for potentially eligible patients for this study. The primary study outcome will be postoperative pain, assessed on a 10-point Likert Scale as well as on the pain burden index. In addition, other PRO instruments will be administered to evaluate QOL measures including symptom assessment, decision quality, body image, and anxiety to better understand the overall benefits and harms of a GCC approach versus an AS approach.

Aim 2. Measure the incremental utility of GCC compared to AS according to a preference-based quality-adjusted life year metric (QALY).

We have developed an 8-item questionnaire based on a time trade off model to collect a preference-based measure of health on the cohort in Aim 1. This tool will be included in the patient survey and data collected from this tool will be used to compare a standardized health utility measure of GCC versus AS. This deliverable will allow patients and stakeholders to better weigh the benefits and tradeoffs of each approach.

3.0 RESEARCH SUBJECT SELECTION:

This study will be conducted at 6 NCI Comprehensive Cancer Center sites (DUMC, DFCI, MDACC, MGH, NWH, and DFCI @ SSH). Additional study sites may be considered to enhance accrual.

The GCC group will be those patients diagnosed with DCIS and treated according to one of the standard treatment options for DCIS (Table 1). Importantly, since only 2-3% of all women diagnosed with DCIS are offered and/or undergo active surveillance, there are insufficient numbers of women with DCIS solely electing AS to compare with women treated according to GCC, even across 3 large volume cancer centers. Therefore, we decided to add to our DCIS AS group, those patients who have a similarly high breast cancer risk based on a diagnosis of ADH, ALH, or LCIS for whom the routine recommendation is active surveillance. The ADH/ALH/LCIS group will thus serve as an additional proxy for the DCIS active surveillance group, since these risk lesions are managed with a follow up and surveillance approach as could be applied if AS were to be used for low risk DCIS. This design will allow the most relevant comparison of PROs between GCC and AS strategies for conditions associated with increased breast cancer risk.

English and Spanish speaking patients diagnosed for either: DCIS, ADH, ALH and/or LCIS between 2012 and 2016 will be included. Each site has a large patient volume of DCIS cases treated and specific expertise in studying a DCIS patient population. Moreover, the sites have unique and complementary patient populations, with a large African American population treated at DUMC (26.7% of all patients with DCIS treated 2011-2013) and a sizable Hispanic population treated at MDACC (12.8% of all patients with DCIS treated 2011-2013).

Eligibility Criteria. Patients treated at DUMC, DFCI, MDACC, MGH, NWH, or DFCI @ SSH with a diagnosis of DCIS, LCIS, ADH, or ALH who are also:

- Age 18 or more at index diagnosis
- Diagnosed with DCIS, LCIS, ADH, or ALH (the most recent, highest risk lesion is the "index lesion") between January 1, 2012 and June 30, 2017
- Able to read either English or Spanish and able to provide written (via paper), verbal consent or on-line informed consent
- Treated and followed at one of the study sites (including affiliated network sites) and for whom treatment and surveillance data are available, for at least 1 year of follow up after date of diagnosis
- Participants with bilateral synchronous or metachronous disease (DCIS, LCIS, ADH, ALH) are eligible

Exclusion criteria

- Ever had a diagnosis of invasive or microinvasive breast cancer
- DCIS prior to index lesion or history of progressive/recurrent DCIS after treatment
- Other cancers (excluding non-melanoma skin cancer) diagnosed within 5 years prior to index

lesion, including concurrent invasive cancer diagnosis and up to the present time of participant's approach to invitation into the study
- Patients identified by treating physician as being unsuitable for contact

4.0 RESEARCH SUBJECT ENTRY

All activities will be conducted through the 6 study recruitment sites, who will handle all eligibility for their own site's patients. The DFCI main study site will screen and recruit for its own patients as well as for DFCI @ SSH patients. Patients will be recruited individually to the trial. All women with DCIS, LCIS, ADH or ALH newly diagnosed between January 1, 2012 and June 30, 2017 and treated at one of the 6 designated study sites will be identified systematically at each study site using cancer registry and clinic, radiology, and pathology record review. We will collect consecutive cases in a retrograde fashion starting from June 30, 2017 to January 1, 2012 until we have collected 900 DCIS cases and 300 LCIS, ADH, or ALH cases.

In order to assess eligibility and initiate entry into the study chart review necessary for Aim 1 of the study, we will request approval of a waiver of informed consent and a waiver of HIPPA. Once approved, a research coordinator at each site will review clinic, radiology, pathology, and tumor registry lists to screen for potential candidates, and identify potentially eligible patients. We will extract the following from the medical record for potential participants:

- Name
- Contact information (i.e. mail address, phone number and/or email address)
- Age
- Race/Ethnicity
- Date and type of last biopsy
- Date and type of last surgery
- How lesion identified and relevant mammography
- Pathologic features of the disease on core biopsy (if DCIS: grade, necrosis, ER, PR/HER2 if done, size, microinvasion)
- Type of subsequent evaluation of lesion (excision, surgery etc.) and any subsequent breast pathology or procedure
- Any adjuvant treatment
- Date and vital status at last follow-up; we will plan to complement this with a National Death Index (NDI)/Institutional database look to make sure potential participants are available before contacting them.

Sites responsible for screening patients and their affiliates will use the eligibility information above for their patients to determine eligibility. We will also use these data to describe the patient population and the disease characteristics of these non-invasive breast lesions at diagnosis.

For each eligible case determined through this rigorous review, the institutional attending physician will be notified by email about the study and the plans to invite the patient to participate in the survey study. Staff at each study site or the lead site for affiliates will contact the treating physician to ask them to indicate if they have any concerns about contacting this patient for the study. If the local treating physician does not indicate any potential problems with the selected patient's participation within 2 weeks, then the study coordinator at each site will verify the mailing address for each eligible patient.

Each site will send their own potential patients the study invitation letter (Appendix A) which will include information about the study, provide study contact information, and ask patients to respond, and if interested in participating in the study, write their email address, or alternative form of contact. Because people are busy and may respond to different forms of communication (i.e. calls, notes, letters, etc.), the local study team will follow up with 3 additional contacts over an 8-week time period (2 weeks (recontact), 4 weeks (call/resend) and 8 weeks (call/resend) to allow for sufficient time to respond. The DFIC study team will pilot two patient outreach materials from Patient Advocates—two brief notes—added to the invitation letter and survey to one hundred patients to test improved response and participation outcome. One or both of these outreach material, if proven effective, may be continued past the pilot one hundred patients. At the end of the recruitment period when no further new surveys are to be initiated, the DFCI study team will inform by mail, email, or phone any new patient who indicates interest to complete a survey that the study is closed and no new surveys will be initiated.

The DFCI study team has found this to be acceptable and desired in past survey research they have conducted. As noted above, initial contact will be made by each recruiting site for their own patients (e.g. MDA study team will contact MDA patients, Duke study team will contact Duke patients and DFCI study team will contact DFCI patients). Collaborating institutions may use waivers of consent and authorization to access patient study records to determine eligibility, collect data from the medical charts and to initiate patient contact for the prospective survey. The names and contact information of all women who agree to participate for the prospective component of this study (the survey) will be sent from the local team (MDACC, Duke, MGH, NWH, or DFCI @ SSH) to the DFCI study team. The DFCI study team will conduct all consenting and survey initiation/follow up, as described in section 5.5.1.

The DFCI study coordinator then will initiate the survey (Appendix B) online, paper or over the phone as requested by the participant. The majority of the surveys will be conducted in English, although a Spanish language paper version of Survey B.1 and B.2 will be available. There will be 3 potential recontact timepoints by the DFCI study staff to participants who do not complete the survey: 2 weeks (recontact), 4 weeks (call/resend) and 6 weeks (call/resend) from the initial mailing.

There are 3 modes in which an English-speaking patient can elect to complete the prospective survey: online, paper or phone. A Spanish speaking patient will have the paper survey available to select. Depending on the way the survey is completed, consent will be obtained accordingly. Please see section 5.5.1 for additional details.

Each site or the lead for an affiliate will track their own patients for eligibility and desire to participate (Appendix A). Sites will then pass contact information and approved CRF information for respondents who affirm interest on Appendix A to DFCI study staff. DFCI study staff then will follow up with patients for consenting and survey participation. See 5.5 Description of the study process for additional survey completion detail.

DFCI study staff will register all consenting participants (DF/HCC and non-DF/HCC) in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101, but registration will occur once a consent has been obtained (paper consent, online elements of consent, verbal consent depending on modality of participant completion) and once the survey has been completed.

DFCI study staff will complete an eligibility checklist according to DF/HCC SOP REGIST-104, for all women who initiate a survey (any modality). If a participant completes a survey via RedCap, study staff will print out the page showing she checked the box saying she agrees to the elements of consent as the documentation of her consent. For participants who complete by paper, DFCI study staff will have participants sign an informed consent document. DFCI study staff will keep documentation of verbal consent for those giving consent over the telephone. DFCI study staff will collect and store participant consent forms and eligibility checklists. The Coordinating Center will provide a study number for all enrolled participants.

5.0 STUDY DESIGN AND METHODS

5.1 Design /study type

This is a one-time, cross-sectional, patient survey study where the overarching goal is to evaluate the benefits and harms of currently accepted GCC vs. AS (including patients with DCIS undergoing AS, as well as patients with ADH or LCIS/ALH as a proxy) for DCIS.

5.2 Selection of Instruments

Rationale for participant selection and survey methodology. Although we recognize that issues of decision-making and treatment selection are more salient closer to the date of diagnosis when these decisions take place, the short timeframe of the project period limits the number of cases that could be identified and surveyed within the timeframe of the study. Therefore, we are reviewing contemporary cases diagnosed from 2012 to 2016 for eligibility. The advantage of this design is that it allows us to assess QOL after diagnosis and treatment in a large group of patients, and provides a more cost-effective approach compared to rapid case ascertainment. Moreover, this design will allow collection of our primary endpoint of persistent, rather than postoperative, pain among the participants, as well as several secondary endpoints, including health-related and psychosocial QOL, anxiety, depression, and intolerance of uncertainty among patients at a range of time in follow-up.

***Survey instrument/predictors*:**

Screening questions: We will ask participants for their first date of DCIS/ADH/LCIS/ALH diagnosis; if they have had additional breast lesions since that initial breast lesion diagnosis; and if she has had any malignancy, other than non-melanoma skin cancer. Please see Appendix E (Screening questions) for reference.

Socio-demographics: Women will be asked about their race, education, employment and financial status using items selected from the **Alliance Patient Questionnaire** that is currently being piloted (Alliance A191401), adapted to include an item on employment status that has been tested previously in a breast cancer population and is going to be added to the next version of the Alliance Patient Questionnaire.

Financial burden: We will adapt items from the National Health Interview Survey[50] and the Cancer Care Outcomes Research and Surveillance (CanCORS) Study[51] to assess financial burden and impact on

employment-related metrics (e.g., sick leave, unpaid time off work).

Medical, treatment, and family history: We will survey women regarding their treatment history, including surgery type, radiation, and hormonal therapy use and adherence[52,53], as well as family history of breast/ovarian history. Specifically, we will adapt Part 1 of the Voils two-part measure of medication adherence, which includes 3 items that evaluates the extent of non-adherence over the past week. [52,53]

We will assess co-morbidities using the Self-Administered Co-morbidity Questionnaire (based on Charlson Co-morbidity Index and other comorbidity indices).[54]

Pain: the presence, severity, and functional impact of pain will be recorded as the primary QOL endpoint. The primary endpoint will be highest pain severity measured on a 10-point Likert scale and Pain Burden Index as measured by the Breast Cancer Pain Questionnaire (BCPQ). The BCPQ includes assessment of pain severity, pain frequency (how many days/week), and pain location (breast, arm, side, axilla), from which a Pain Burden Index (PBI) can be calculated.[22,55,56] The BCPQ also includes questions about other body pain, seeking medical help for pain, and painkiller use. We will also use the Brief Pain Inventory, a well-validated general measure of pain and disability, worst pain, least pain, and interference with activities.

Knowledge: Among patients with DCIS only, DCIS and breast cancer knowledge will be measured with items adapted from the Breast Cancer Surgery Decision Quality Instrument (BCS-DQI), an instrument designed to evaluate the quality of breast cancer treatment decisions.[57] A series of true/false questions used in a prior survey of women with DCIS[58] will also be used to assess knowledge of facts specific to a DCIS diagnosis and treatment; items will be adapted for patients with an ADH/LCIS/ALH diagnosis.

Decision-making: Treatment goals and preferences will be assessed with the BCS-DQI which includes items designed to measure individual patient goals and concerns. [57] Four items (The SURE scale) adapted from the Decisional Conflict Scale will be used to measure patients' uncertainty about which treatment and factors contributing to uncertainty.[59,60] The 5 item Decision Regret Scale will be used to measure decisional regret.[61] Patient perception of the decision process will be assessed using an adapted version of the Control Preferences Scale.[62,63] Communication with physicians and sources of information about DCIS/ADH/LCIS/ALH management options will be assessed using items from a prior study of surgical decision-making.[64]

Risk perceptions: We will assess risk perceptions in women with DCIS, LCIS/ALH or ADH using questions developed by Lerman and Croyle[65] that have previously been used to measure risk perceptions in women with DCIS.[47] This will ultimately be compared to actual risk of their condition based on published data.

Quality of Life (QOL): We will use the SF-12 to measure health-related QOL.[66] A modified 19-item version of the Breast Cancer Prevention Trial (BCPT) Symptom Checklist will be used to evaluate commonly reported menopausal symptoms.[67] The Breast-Q, a validated instrument to evaluate outcomes following surgery, will be used to evaluate satisfaction with appearance, self-image, and sexuality.[68] Four items from the Quality of Life in Adult Cancer Survivors (QLACS) will be adapted to evaluate frequency (1=never; 7=always) of worries about DCIS, including concerns about future breast events and death from DCIS.[69]

Emotional/Psychological: To assess generalized anxiety, we will use the short-form version of the State Trait Anxiety Inventory (STAI) scale.[70] We will use the Center for Epidemiologic Studies Depression (CES-D) Scale to evaluate depressive symptoms.[71] Additionally, we will assess feelings of uncertainty using the Intolerance of Uncertainty Scale (Short-form), which has been used in studies of active surveillance in the prostate cancer setting.[72-74]

Time-trade-off (TTO):[72-74] We will use the QALY metric to compare tradeoffs of GCC versus AS for DCIS as determined by preference-based, as opposed to cost-based, utilities in this patient population. QALYs are derived by multiplying the length of time in a given health state with the health utility (utility weighting) of the given disease/health state. Thus, there are two primary inputs to a QALY calculation: the years of extended life with a given treatment and the health-related quality of life associated with both a pre- and post-treatment state. The general approach to determining QALYs for a given intervention uses the valuation of unaffected individuals to derive societal values for certain disease states. The time trade-off (TTO) model is a method developed specifically for use in health care evaluations and has been validated against the SG method. Respondents choose between perfect health with shorter life expectancy or poorer health but with longer life expectancy. The TTO tool will include an 8-item questionnaire.

Treatment risk trade off:[75,76]
6 additional items adapted from a prior study of treatment preferences, that will ask women to assume a hypothetical risk of developing breast cancer and ask them to quantify the amount of risk reduction it would take for them to choose a particular surgical option (e.g., lumpectomy + radiation, mastectomy).

We anticipate that the entire one-time survey will take participants approximately 30-40 minutes to complete. The survey has been pilot tested with patient advocates to ensure that the survey content is presented in a clear and understandable format and that it is not overly burdensome to respondents. A participant's active duration on study is the length of time to complete this single survey.

5.3 Description of the Survey Methods

We will use a multi-center, cross-sectional patient survey design to systematically collect and compare PROs in patients in the GCC or AS groups. All participants will be asked to complete a one-time, REDCap online survey or a mailed paper survey, depending on patient preference, and a telephone-administered version will be available if necessary.

5.4 Data Collection

PRO data to be collected is described in detail above (Section 5.2). Additional data will be abstracted from the medical record beyond what is needed to determine eligibility, including prior history of breast surgery (lumpectomy, mastectomy, reduction/augmentation, implants, or other surgery, axillary surgery) and known high risk predisposition (e.g., BRCA 1 or 2 positive, prior history of radiation to the chest.

5.5 Description of the study process

5.5.1 Survey Administration

We will recruit approximately 900 women with DCIS matched 3:1 to women with ADH or LCIS/ALH (proxies for AS group) or DCIS choosing AS identified at 6 geographically and demographically distinct study sites: DUMC, DFCI, MDACC, MGH, NWH, and DFCI @ SSH. Any patients who have selected AS for DCIS will specifically be identified and contacted for inclusion in the study. Enrolled patients will be asked to complete a one-time survey. The recruitment and survey phases will take place over an 18-month period once enrollment begins. We anticipate data cleaning and analysis will last 6 months.

The study coordinator at each site or the lead for an affiliate site will verify the mailing address and/or email address for each eligible patient, then local study staff will send an invitation letter and response form (Appendix A). The invitation letter and response form will include information about the study, study coordinator contact information, and will ask participants to send the local site their email address in order to receive the link to the study materials including an online elements of consent information page and online survey (Appendix B), or their address to receive the consent and survey (Appendix B) via mail. The contact information of all women who agree to participate in the study will be sent from the local study team to the DFCI study team to contact potential participants to initiate the consenting and survey process (Appendix B). In DFCI's initial application, it was requested and approved, to have a waiver of documentation of consent for people who complete the survey online or on the phone.

Web-based
The REDCap survey can be accessed from any computer that has internet; the place of completion will be at the discretion of the participant. Prior to the survey questions in REDCap, participants will read and respond to the screening questions (Appendix E) to determine eligibility before moving to a next page which contains the elements of informed consent (Appendix C). If a participant is ineligible to participate in the study, she will not be able to move on to the informed consent information page. If the participant is eligible, she will proceed to the informed consent information page and then to the survey itself (Appendix B).

Print survey
As an alternative to the on-line survey, patients will be provided the option to complete a survey by mail, or by phone. If completing by mail method, the patient will be mailed two copies of the paper consent, and asked to sign one of the copies and return with the completed survey. The paper version of the survey (Appendix B) will be sent with the screening questions (Appendix E) as a cover page along with the two copies of the paper informed consent form. If the participant answers the screening questions (Appendix E) and is ineligible, she will be instructed to stop and return Appendix E in the enclosed pre-paid, pre-stamped envelope. If the participant is eligible, she will be asked to sign one copy of the consent and return it along with the completed screening questions (Appendix E) as well as the completed survey (Appendix B), which will be attached to one-another for the paper version.

Phone survey
If completing by phone, the study team will first verbally introduce the study, then will administer the screening questions (Appendix E). If the participant is ineligible, study staff will not continue onto the survey. If the participant is eligible, the study coordinator will administer and document verbal consent (Appendix D) and subsequently administer the patient survey (Appendix B).

The online survey will be programmed in REDCap with appropriate skip patterns, and the paper version

will have clear instructions in order to reduce missing data. The paper copy of the survey is submitted as Appendix B. There will be 10 different versions of TTO questions in paper and in REDCap. Participants will be assigned to different versions of TTO (Treatment Trade Off) by the DFCI study team on a rolling basis (e.g. first participant will receive the first version, second participant will receive the second version, and so on). TTO survey is submitted as Appendix G. Patient advocates have piloted both the online and written form of the survey. If the survey needs to be further revised, the study team will submit an amendment at DFCI and upon IRB approval, external sites will submit through local IRBs. Once the survey has been finalized, it will be disseminated to participants by the DFCI study team.

Methods and Frequency of follow-up: In order to reach a broad sample of patients who may be eligible for this study, the local study team will mail an initial letter (Appendix A) to a prospective patient. Because people are busy and may respond to different forms of communication (i.e. calls, brief insert notes, letters, etc.), the local study team will follow up with 3 additional contacts over an 8-week period to allow for sufficient time to respond. The DFIC study team will pilot two patient outreach materials from Patient Advocates—two brief notes— added to the invitation letter and survey to one hundred patients to test improved response and participation outcome. One or both of these outreach material, if proven effective, may be continued past the pilot one hundred patients. The DFCI study team has found this to be acceptable and desired in past survey research they have conducted. Participants who do not respond to Appendix A- Invitation letter and response form will be contacted at: 2 weeks (recontact), 4 weeks (call/resend) and 8 weeks (call/resend). If a participant returns Appendix A, her contact information and select case report form (CRF) information will be sent to the DFCI study team. Please see section 4.0 for the patient contact procedure after the study has closed to respond to patients who indicate interest to complete a new survey.

As outlined above, depending on modality of survey completion, the DFCI study team will collect the information as she is eligible, including: the screener, consent information and survey via her preferred method. There will be 3 potential recontact timepoints by the DFCI study staff to obtain consent/screener/survey from potential participants who do not complete the survey: 2 weeks (recontact), 4 weeks (call/resend) and 6 weeks (resend) from the initial contact. Participants who prefer to complete the survey via telephone will be mailed a copy of the paper survey and contacted up to 3 times to schedule the call to complete the survey.

***Translation of surveys*.** The surveys will be offered in English, although a Spanish translation of Survey B.1 and B.2 will be available in paper format for mailing to patients. Translated documents will be submitted for IRB review prior to implementation. We will follow a method that ensures comparable levels of validity, reliability and cultural meaning. First, the English version will be translated into Spanish. Bilingual staff will then review the translation. We have expertise on the study team to lead this task. Certificates of translation will be obtained and submitted to the IRB with the translated material. Native speakers of other languages will be able to participate through a medical interpreter. All patients for whom English is not their primary language who have questions about the survey or study will also be able to utilize our institutional interpreter services.

5.5.2 Special Concerns

***Data Security*.** The web-based survey has been developed in Research Electronic Data Capture (REDCap), a secure web-based software system that is compliant with HIPAA standards. Available to Duke, DFCI, MDACC, MGH, NWH, and DFCI @ SSH faculty, REDCap is commonly used for building and managing online databases and surveys. REDCap provides researchers with features that

facilitate both analytic and administrative competencies. These includes automated data download to Excel and common statistical packages (SPSS, SAS, Stata, R), a built-in project calendar, a scheduling module, and branching logic and range checks to reduce the potential of errors. Ad hoc reporting tools are available including frequencies and reports that can be generated at any time. The REDCap data centers are monitored 24/7 by an experienced team of engineers. They offer data redundancy through replicated databases and offer daily secure offsite backups.

Data Privacy. Only administrators, designated study staff, and customer/technical support managers will have access to survey data which will be stored in a password protected account. A written request from the patient to permanently remove all response data from the account will be answered in no more than two business days. If requested, all files, database records, and backups of this data will be destroyed. Data cannot be recovered after this is performed.

Participant data that is collected and stored in REDCap can be archived, which takes it offline and removes it from the DFCI study staff's list of projects. Once archived, it can only be accessed again by clicking the Show Archived Projects link at the bottom of the My Projects page.

5.5.3 Compensation

As part of the informed consent process, participants will be notified that they will be offered a gift card worth $20 as a token of appreciation for completion of the survey. This gift card will be mailed to them by Dana-Farber Cancer Institute study staff after survey completion.

5.6 Adverse Reactions and Their Management

5.6.1 Reporting Adverse or Unanticipated Events

Should there be a loss of confidentiality, reporting to the IRB will be performed in accordance with required policies.

5.6.2 Anticipated Reactions

The survey being administered entails minimal physical and psychological risk on the part of the participants; however, it is also possible that answering certain questions might cause some distress. The CES-D will be scored within a week of receipt. Patients scoring ≥ 16 will be mailed a letter developed by Patient Advocates, Study PIs, and the CRC Staff within one calendar month providing support resources.

There is the potential loss of confidentiality, which will be managed by adherence to HIPAA regulations at all study sites.

5.6.3 Reaction Management

It is possible that answering questions related to breast conditions may cause anxiety. In the letter of introduction, women are notified that they are free to skip any questions they do not want to answer.

Additionally, women are advised to contact their physicians or a study representative with any questions or concerns. If necessary, study staff will provide information on counseling services to patients that request assistance.

All members of the study team will be required to complete Human Subjects Protection Training. This requirement may be met by completing the NIH course, the CITI (Collaborative Institutional Training Initiative) program or another course as required by the member institution.

6.0 STATISTICAL ANALYSIS

6.1 Primary and secondary endpoints

Endpoints were selected with the input of patient stakeholders in the general categories of: 1) breast cancer and health-related clinical outcomes including pulmonary, cardiovascular, other cancer, and hematologic disease), and 2) Patient Reported Outcomes (PRO) which will include comprehensive domains of QOL and psychosocial outcomes, with a primary focus on pain and physical symptoms.

6.2 Sample size and statistical power

Importantly, published data indicate that patients undergoing lumpectomy with radiation report comparable levels of pain and sensory disturbances as those undergoing mastectomy.[56] Thus, these treatment groups will be grouped together in the initial analysis, then a stratified analysis will be performed. Preliminary data among 582 women undergoing either lumpectomy or mastectomy indicate that the mean persistent pain intensity after breast surgery is 2.61 (DS 4.24).[55] Given a sample size of 900 patients in the GCC group and 300 in the AS group, we will be able to detect with 90% power at a level of 0.05 (2-sided) a difference in pain intensity score of 2 (from 2.61 to 0.61), which has been deemed to be a clinically meaningful difference.

Based upon the number of unique cases diagnosed with DCIS at each site between 2010 and 2013, we estimate that at all 6 study sites combined, approximately 1500 women will have been diagnosed with DCIS between January 1, 2012 and June 30, 2017 and will be eligible to participate. Our response rate in prior survey studies has been approximately 60% using the approach we will adapt to the current study; thus, we anticipate that about 900 women with DCIS will be accrued and will complete the survey across all study sites. These patients will be matched 3:1 to participants diagnosed with ADH or LCIS/ALH undergoing active surveillance. DCIS participants will be matched 3:1 to ADH/LCIS/ALH participants, based on matching criteria of age within 5 years, year of diagnosis, and study site. Additional matching criteria such as race, income, highest education level attained, and family history of breast cancer will be considered based upon stakeholder input during the protocol preparation process.

6.3 *Analysis Plan: General Approach.*

We will conduct descriptive analyses to profile the samples, including examination of proportions, means, and medians, as well as estimates of variability such as standard errors, ranges, and confidence intervals. We will identify outlying observations. Continuous data distributions will be evaluated for appropriateness of scale, and normal score transformations will be used where appropriate. Appropriate summary statistics, histograms, scatter plots, or one- or two-way contingency tables for women of each

ethnic group will be computed. These analyses will be followed by bivariate analyses to examine the pairwise relationships among variables under examination. Demographic data will be compared for the respondents and non-respondents using chi-square or t-tests to assess selection bias. In addition to baseline disease and socio-demographic data, information relating to other treatment (e.g., endocrine treatment, radiation) as well as co-morbidities will be collected, allowing us to control for potential confounding by these factors. We will also analyze the decision-making, DCIS knowledge, and risk perception data at baseline and compare these domains between the GCC and ADH/LCIS/ALH/AS groups. We will also systematically collect and evaluate and report on the upstaging rates and associated details from initial diagnosis of DCIS.

6.4 ***Management of missing data:*** As with all studies there is a risk of biased statistical inference with missing data and we will adhere closely to standards put forth by the National Research Council. [77] We will include details about missing patient data in all tables in subsequent analyses, and include a comparison of baseline characteristics of patients with and without missing data. We will carefully consider whether data missingness is random or whether missingness may be attributable to a certain factor and therefore not random (e.g., older women may be less likely to answer questions). We will assess non-response bias by comparing available characteristics in both patients and providers (e.g., practice type) among responders and non-responders.

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