Genotypic and Phenotypic Predictors of Cancer Therapy Adherence and Symptom Trajectories in Women with Breast Cancer

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Aromatase inhibitors (AI) such as anastrozole effectively prevent hormone receptor positive breast cancer (HR+BC) recurrence but suboptimal AI adherence is a problem linked to AI-related, highly-variable symptoms, which may have biological underpinnings. This dissertation study is an ancillary study of prospectively-collected data from parent observational studies. This study combined parent study data from postmenopausal women prescribed anastrozole for HR+BC with symptom data (N=360), adherence data (N=291), and banked biospecimens (N=122). This study identified distinct subgroups using group-based trajectory modeling (GBTM) based on self-reported symptom and anastrozole adherence trajectories over the first 18-months of therapy (Aim 1), identified combined symptom and adherence trajectories (Aim 2); and explored whether genotypic and phenotypic factors (e.g., demographic, clinical) were associated with trajectory group membership (Aim 3). Using neuropsychological symptom data (N=360) collected at pre-anastrozole, 6-, 12-, and 18-months post-initiation, we found five distinct trajectories of neuropsychological symptom burden (NSB)—low-stable, low-increasing, moderate-stable, high-stable, and high-increasing (Aim 1). Anastrozole adherence data (N=291) collected via electronic event monitoring (MEMS®) were measured continuously for 18 months. We used monthly calculations for GBTM and found five trajectories: very low, low, high/sharp decrease, high/slow decrease, and persistently high (Aim 1). Most women were adherent; however, within five months, anastrozole adherence was at or below 80% in more than one-third of the sample. The relationship

between NSB and adherence trajectories were examined simultaneously using a dual GBTM in 291 women (Aim 2). After NSB trajectories were re-evaluated for the 291 sample, a dual trajectory analysis suggested a bidirectional relationship between NSB and anastrozole adherence. However, for most women, taking anastrozole does not result in increased neuropsychological symptom burden. Phenotypic risk factors (Aim 3) to predict trajectories with greater NSB (N=360), included younger age and baseline (pre-anastrozole) medication use, including anti-depressants, non-narcotic analgesics, narcotic analgesics, anti-anxiety, and no calcium/vitamin D use. Protective factors for women in the higher (better) adherence trajectories (N=291) included not using thyroid medications or antidepressants. Younger age predicted greater NSB in the dual GBTM. Genotypic factors for greater NSB were *PGR* rs471767 and *ESR1* rs1884051. Genotypic factors for greater adherence were *ESR1* rs985694 and *PGR* rs1942836.

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Preface

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1.0 Dissertation Proposal

Section 1.0 consists of the dissertation proposal, which was approved by the committee at the comprehensive examination and overview.

1.1 Specific Aims

More than 3.8 million US women are living with breast cancer (BC) (Miller et al., 2019), and most tumors are hormone receptor positive (HR+) (N. Howlader et al., 2014; Howlader et al., 2018). Current standard of care is a 5-year course of endocrine therapy with an aromatase inhibitor (AI) to reduce recurrence and progression risk to less than 10% for early-stage HR+BC in postmenopausal women (Bradley et al., 2015; Cuzick et al., 2010; B Makubate et al., 2013; NCCN Guidelines Panel, 2020). Despite this, suboptimal medication adherence is a significant issue largely due to adverse symptoms associated with AIs (Murphy et al., 2012; Sawesi et al., 2014). Specifically, an estimated 23% to 30% of women prescribed endocrine therapy do not fill their initial prescription (Bowles et al., 2012; Camacho et al., 2017), self-reported adherence to once daily AIs is as low as 48% in the first year, and adherence decreases with each year of therapy (Bender et al., 2014; B Makubate et al., 2013; Ziller et al., 2013). However, little information exists for temporal patterns of AI adherence – and existing studies seldom objectively measure adherence (Sawesi et al., 2014), instead using less reliable self-report, patient recall, or pharmacy refills (Dunbar-Jacob et al., 2010; Dunbar-Jacob et al., 2012; Oberguggenberger et al., 2012; Sawesi et al., 2014). Nevertheless, suboptimal adherence is associated with poorer outcomes in this

population (B Makubate et al., 2013). Further, numerous studies have related AI adherence to symptoms, but few studies have used an adherence measure with objective dose timing (Bright & Stanton, 2019) and temporal comparisons with symptoms (Bright & Stanton, 2018), leaving the nature of this AI-symptom relationship and variability among women largely unexplained.

Women report disease- and treatment-related symptoms and AI-related side effects, herein called symptoms, as the primary reason for suboptimal AI adherence (Aiello Bowles et al., 2012; Bender et al., 2014; Lintermans et al., 2014; Murphy et al., 2012; Sawesi et al., 2014; Wouters et al., 2014). Nearly every woman with BC who receives an AI reports experiencing at least one symptom, and symptom phenotypes and severity are highly variable among women (Aiello Bowles et al., 2012; Beckwee et al., 2017; Boonstra et al., 2013), but the source of symptom variability is not known. Symptoms research has traditionally been cross-sectional or retrospective and, if prospective, has not included a pre-therapy assessment. Measuring symptoms pre-therapy, as well as prospectively, aids in assessing changes to symptoms over time. Examining temporal patterns of AI-related symptoms may inform intervention timing and identify differences among women's symptom phenotypes. The high symptom variability among individuals suggests mechanisms of symptoms experienced during AI therapy which may, in part, be due to biological underpinnings (Liu et al., 2016; Thummel & Lin, 2014; Wilkinson, 2005). Factors in AI (anastrozole, letrozole, exemestane) absorption, distribution, metabolism, and elimination (ADME) pathways and their resulting symptoms are not entirely clear. Symptom variability may arise from genes associated with a woman's AI ADME pathway (Gervasini et al., 2017; Hamadeh et al., 2018; Lynch & Price, 2007; Tannenbaum & Sheehan, 2014). Additional medication regimens may also moderate the influence of ADME on the relationship between AI adherence and symptoms (Lynch & Price, 2007; Tannenbaum & Sheehan, 2014). Discovery cohorts have

explored the roles of genomics in symptoms, toxicity, and therapeutic response with mixed results (Baatjes et al., 2017; Gervasini et al., 2017; Hamadeh et al., 2018; Lintermans et al., 2016). Most of the studies have failed to account for the extent of adherence. Few studies have evaluated genomic influence on ADME of anastrozole independently evaluated, rather than grouped with other AIs (letrozole, exemestane) (Colomer et al., 2008; Garcia-Casado et al., 2010; Gervasini et al., 2017; Lintermans et al., 2016; Napoli et al., 2013; Shao et al., 2015). ADME genotyping is a useful clinical tool, which has been used to tailor health care for other drug classes (Cavallari et al., 2018; Elsensohn et al., 2017; Empey et al., 2018), and it has changed practice to dramatically improve patient outcomes. For example, cardiovascular research studies have focused on drug efficacy and/or prevention of symptoms with clopidogrel-*CYP2C19* metabolizer gene (loss of function allele, poor metabolizer phenotype, associated with increased risk of thrombosis) and simvastatin-*SLO1B1* drug transport gene (homozygous C allele associated with increased risk of myopathy) (Tuteja & Limdi, 2016).

We hypothesize that (1) women taking anastrozole (an AI) can be phenotypically classified into distinct subgroups based upon their symptom experience and adherence; and (2) that there is a relationship between these classifications. Additionally, we will explore whether the classifications are modified by covariates, e.g., phenotypes and ADME genotypes.

The following are the specific aims for our study in a sample of postmenopausal women prescribed anastrozole for early-stage HR+BC.

Aim 1. Identify distinct subgroups of women based on self-reported symptoms trajectories and anastrozole adherence trajectories over the first 18 months of therapy. Using previously collected symptom and adherence data in a well-characterized sample of women, we will determine distinct latent classes of women by their symptom trajectory using finite mixture

modeling, which will be described in more detail in the analysis section. We will identify temporal patterns and distinct latent classes by the symptom trajectories of women's self-reported physical and psychological symptoms, including those associated with pain, anxiety, fatigue, depression, sleep, and economic hardship, collected prospectively pre-therapy and at 6, 12, and 18 months. Electronic event monitoring (MEMS®) will continuously measure anastrozole adherence for 18 months and will reveal daily anastrozole adherence patterns (calculated as days correct/days prescribed x100), aggregated monthly (continuity, change, patterns, and timing), also using finite mixture modeling.

Aim 2. Identify distinct subgroups of women based on combined symptom and anastrozole adherence trajectories. Symptom and adherence patterns will be examined concurrently using finite mixture modeling with the dual (symptom and adherence) trajectories.

Aim 3. Explore whether genotypic factors (e.g., germline, or heritable, genomic variation associated with anastrozole ADME pathway) and phenotypic factors (e.g., demographic, clinical) are associated with predicted group membership for a) *symptom trajectories,* b) *adherence trajectories, and* c) *the relationship between symptom and adherence trajectories together.* We will generate genotypes for candidate genes using previously collected, banked samples, as well as phenotypic factors (participant and clinical) from previously-collected, prospective data, to evaluate their potential role as risk factors for symptoms experienced and suboptimal adherence.

Identifying temporal instances of symptoms and adherence (Aim 1) and their potential relationship (Aim 2) will inform intervention development and timing. The overarching goal of this research is to provide evidence to enable clinicians to proactively manage anastrozole adherence and symptoms with targeted interventions by identifying critical timepoints for

intervention (Aims 1 and 2) and women at risk (Aims 3a-c). Assessing genotypic and phenotypic factors is a precision health strategy, which will lay the groundwork to shift the AI therapy paradigm from a symptom-reactive to a symptom-proactive and adherence-proactive approach. This study will fill scientific gaps by characterizing adherence and symptom patterns over time, including the biological role of the anastrozole ADME pathway.

1.2 Background and Significance

1.2.1 Breast Cancer is Most Prevalent in Postmenopausal Women, and Millions are Survivors

In the United States (US), one of eight women will be diagnosed with breast cancer (BC) in their lifetime (Howlader et al., 2019; U.S. Cancer Statistics Working Group, 2018), most are postmenopausal at the time of diagnosis, and at least 70% of their tumors are hormone receptor positive (HR+) (N. Howlader et al., 2014; Howlader et al., 2019). The 5-year survival rate for breast cancer is approximately 90%; consequently, the number of women living with BC is high at 3.4 million (Howlader et al., 2019).

1.2.2 Aromatase Inhibitors Effectively Prevent BC Recurrence and Progression

To prevent tumor disease recurrence and progression in postmenopausal women with hormone receptor positive (HR+) BC, current guidelines include adjuvant aromatase inhibitor (AI) therapy in a once daily standard dose regimen for a minimum of five years (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2015; Gnant et al., 2017; Pan et al., 2017; Runowicz et al., 2016). AI therapy prevents BC recurrence and progression via aromatase inhibition, which blocks conversion of adrenal and ovarian androgens to estrogens (Figure 1) (Whirl-Carrillo et al., 2012).

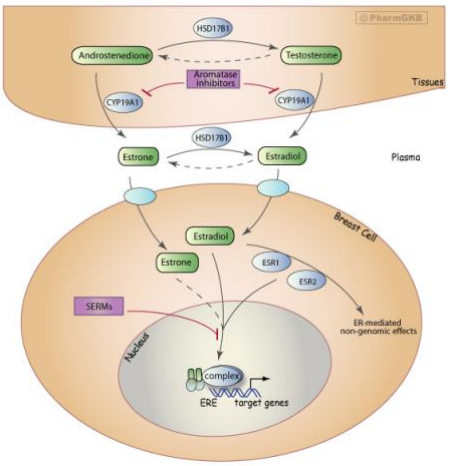

Figure 1 Aromatase Pathway

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Current AIs used in the US are anastrozole, letrozole, and exemestane (Table 1) for drug characteristics). Unlike exemestane, anastrozole and letrozole are nonsteroidal, competitive AIs, but all three are primarily metabolized in the liver (*Anastrozole*, 2021; Buzdar, 2003; *Exemestane*, 2020; *Letrozole*, 2020). Of the three AIs, Anastrozole has the longest half-life of 50 hours and reaches a steady-state after seven days of daily dosing (*Anastrozole*, 2021).

Table 1 Aromatase Inhibitor (AI) Characteristics

Characteristics	Anastrozole	Letrozole	Exemestane
Type	Nonsteroidal, type 2 inhibitor (competitive)	Nonsteroidal, type 2 inhibitor (competitive)	Steroidal, type 1 inhibitor (non-competitive)
Standard dose	1 mg/day	2.5 mg/day	25 mg/day
Maximum E2 suppression	2-4 days	2-4 days	7 days
Steady-state	7 days of daily dosing	60 days of daily dosing	7 days of daily dosing
Half-life	50 hours	2 days	24 hours
Activity	Reversible	Reversible	Irreversible, enzyme activity blocked permanently
Metabolism	Liver N-dealkylation, hydroxylation, and glucuronidation	Liver CYP3A4 and CYP2A6 pathways	Liver CYP3A4 pathway
Excretion	Feces, some urine	Urine	Equally feces, urine

Research confirms removing the proliferative stimulus for an HR+ tumor with endocrine therapy will result in a substantial decrease in disease free survival (recurrence/progression) at five, ten, and even twenty years (Bradley et al., 2015; Cuzick et al., 2010; Pan et al., 2017). To confirm AI treatment efficacy, suboptimal adherence to this prescribed medication regimen is associated with lower rates of disease-free survival in this population (Chirgwin et al., 2016; B Makubate et al., 2013). And though at least one study found no relationship (Weaver et al., 2013), adherence to a complete AI therapy course is considered crucial (B Makubate et al., 2013; Pan et al., 2017). It deserves mention that, in addition to disease-free survival and delay of progression, consideration for quality of life outcomes related to symptoms of concurrent and subsequent therapies is also indispensable (Fallowfield, 2007; Haidinger & Bauerfeind, 2019; Martino et al., 2020).

1.2.3 Suboptimal Adherence is a Major Problem in AI Therapy

Adherence is defined as the extent to which a patient carries out the agreed upon treatment (World Health Organization, 2003). Similar to medication adherence in other chronic diseases, adherence is suboptimal for AI therapy. Up to one third of women do not fill their initial AI prescription (Bowles et al., 2012; Camacho et al., 2017), and adherence to AIs averaged 48% (confidence interval 35-62) in the first year (Kesmodel et al., 2018; Ziller et al., 2013). Additional decreases in adherence occur in years 2-5 (Bender et al., 2014; Hadji et al., 2013; B Makubate et al., 2013). A systematic review of adjuvant hormonal therapy reported a prevalence for adherence between 41-72% and discontinuation at 5 years between 31-73% (Murphy et al., 2012). Consequently, evidence indicates a substantial proportion of women are not fully adhering to their prescribed 5-year AI regimen, and, over time, well under half of the women prescribed AI therapy

complete the course. Regrettably, though adherence is recognized as a concern, the National Comprehensive Cancer Network (NCCN) guidelines provide no guidance on how to improve AI adherence (NCCN Guidelines Panel, 2018), and with biologic and immunologic cancer therapies placing oral therapies in patients' hands, adherence will play a major role in future therapeutic response rates.

1.2.4 Reported AI Adherence Rates Often Depend on the Measurement Method

Adherence literature has primarily relied on self-report or retrospective data, with few studies using an objective adherence measure (Ayres et al., 2014; Sawesi et al., 2014). Adherence can be measured by self-report (survey or diary), medication possession ratios (MPR) from refill claims data, pill counts, biospecimens (drug, metabolite, or drug target levels), and electronic event monitoring (Dunbar-Jacob et al., 2010; El Alili et al., 2016). Self-reported adherence measurement often results in overestimation of the true adherence (Dunbar-Jacob & Rohay, 2016; Dunbar-Jacob et al., 2010; El Alili et al., 2016; Stirratt et al., 2015). This discordance between self-report and objective adherence measures was confirmed in a sample of women with breast cancer (Bright & Stanton, 2019). Thus, studies which have not used objective adherence measures have likely overestimated AI adherence. One study that set out to test a one-question self-report AI adherence measure found that a 'yes' response to having taken an AI in the previous month was associated with estrone and estradiol suppression as measured by blood levels (Brier et al., 2015). However, it should be noted that using hormone levels to assess AI adherence is fallible. First, there are several factors can affect estrogen levels—weight, alcohol consumption, activity, and hormone replacement (Endogenous Hormones and Breast Cancer Collaborative Group et al., 2011).

Additionally, genetic variation can potentially impact AI's effects on hormone levels (Daniel L Hertz et al., 2017; D. L. Hertz et al., 2017).

Electronic event monitoring (MEMS®) is considered a highly reliable approach to objectively measuring adherence, and it is the closest adherence measure to a "gold standard" (Bright & Stanton, 2019). The MEMS® is a medication bottle cap with an electronic chip that time and date stamps each pill bottle opening. Time and date stamps are then summarized as a proportion/percentage: correct doses taken/doses prescribed x 100. Limitations for MEMS® are that participants who use a pill minder cannot effectively use the MEMS® and that the MEMS® cannot confirm that the medicine was ingested at the time of opening. For example, a participant might have opened the bottle to fill it with medicine or the participant might have taken more than one dose per opening. Still, MEMS® provides a report of daily patterns of adherence not seen in self-report, biospecimens, or MPRs. MEMS® provides crucial detailed information about adherence patterns post-AI initiation and throughout the regimen. Since MEMS® also has limitations, it is beneficial to measure adherence with an additional measure. Complementing MEMS® with a subjective adherence measure is a more comprehensive approach to measuring adherence. Questioning participants about MEMS® use can help to determine ability and willingness to use the MEMS®, as well as identify adherence barriers and choices made by the women. For example, if a participant did not fill the bottle and noted that she could not get to the pharmacy, that would be noted as a barrier. This detailed adherence information is needed to inform timing of future intervention delivery. While the adherence measurement type (subjective versus objective) influences the recorded adherence rates in studies, symptoms women experience when taking AIs are a major contributing factor to AI adherence.

1.2.5 AI-related Symptoms May Appear Soon After Initiation

Anastrozole is a selective nonsteroidal AI that decreases estradiol levels by 70% within 24 hours and by 80% after daily use for 2 weeks, reaching a steady state within one week (Buzdar, 2003; Kelly & Buzdar, 2010). The precipitous estrogen reduction associated with AI therapy may produce symptoms as diverse as arthralgias, dizziness, hot flashes, fatigue/asthenia, weight gain, bladder problems, mood or mental changes, headaches, depression, pain, and more (*Anastrozole*, 2021; Drugs.com, 2000-2018). The rapid onset of symptoms may detrimentally affect AI adherence, but to date, there is little information on adherence immediately post-initiation to pinpoint when adherence begins to falter. In addition to physical symptoms, higher AI drug costs have been associated with lower AI adherence suggesting that higher costs may make it more difficult for women to continue their therapy (Farias & Du, 2017; Hershman et al., 2014; Neugut et al., 2011).

1.2.6 AI-related Symptom Type and Severity are Highly Variable

While nearly all women taking an AI will report symptoms (Aiello Bowles et al., 2012), women experience a wide spectrum of symptom phenotypes. BC survivors reported an average 8.9 symptoms, although attribution of the symptoms to endocrine therapy was not established (Rosenberg et al., 2015). Few studies have fully characterized the highly variable symptom phenotypes experienced by women with breast cancer as many studies have focused on one type of symptom and rates differ (Lintermans et al., 2014; Schover et al., 2014). For example, a meta-analysis of AI-induced arthralgia found prevalence rates between 20-74% (Beckwee et al., 2017), while other studies reported sexual dysfunction rates between 36-93% (Aiello Bowles et al., 2012;

Schover et al., 2014). Symptom prevalence rates differ by type, and their rates change over time (Kyvernitakis et al., 2014). AI-related symptom severity also varies among women, though it is not often reported or assessed (Zhu et al., 2019). This study will examine self-reported psychological and physical symptoms related to endocrine therapy, as well as more specific measures of pain, anxiety and fatigue, depressive symptoms, sleep, daytime sleepiness, and perceived economic hardship over time and their relationship to anastrozole adherence (Table 2).

Table 2 Operationalization of Self-reported Symptom Measures, Description, and Concepts

Measure	Description	Concept Measured
Breast Cancer Prevention Trial (BCPT) checklist	42-item survey of the previous 4 weeks Total score and 8 subscales 5-point Likert scale symptom absent: 0 'not at all'; or symptom present: 1 'slightly'; 2 'moderately'; 3 'quite a bit'; and 4 'extremely'	Self-reported physical and psychological symptoms
Brief Pain Inventory (BPI)	11-item survey 0-10 scale with higher scores indicating more pain or interference	Pain level pain interference w/activity
Profile of Mood States (POMS)	anxiety subscale and fatigue subscale to describe feelings or mood using a Likert '0= not at all' to '4=extremely'	Anxiety and fatigue
Beck Depression Inventory-II (BDI)	21-item measure of depressive symptoms, often used clinically	Depressive symptoms
Pittsburgh Sleep Quality Index (PSQI)	Sleep times, hours, and Likert scaled questions assess sleep quality for past month	Sleep
Epworth Sleepiness Scale	8-item 4-point Likert 0 = 'Would never doze' to 3 = 'High chance of dozing'	Daytime sleepiness
Psychological Sense of Economic Hardship	20-item patient report of financial distress with Likert response subscales of financial strain, inability to make ends meet, and not enough money for necessities, followed by several yes/no item responses	Financial strain

1.2.7 Measurements and Timing Matter

Methods-related factors in studies of AI therapy have slowed progress in AI symptom research. One study examining endocrine therapy symptoms, in which 83% of the sample used anastrozole, examined patient-reported outcome measures and showed that prevalence rates (e.g., hot flashes, night sweats, vaginal symptoms, breast tenderness, low libido, diarrhea, nausea, headaches, dizziness, mood swings, and lack of energy) significantly differed from those reported

in clinical trial rates via other participant self-report or clinician report measures (Oberguggenberger et al., 2011). These findings suggest the measure (or perhaps the study purpose) used may influence symptom reporting. Measurement timing is also crucial. Many examined symptoms retrospectively via electronic health record or asked patients to recall symptoms, both of which have limitations. Symptoms should be measured prior to the initiation of treatment, to establish a baseline value. However, few studies have a baseline measurement, thereby limiting the temporal characterization of the symptoms. Preceding therapies can result in cumulative, lingering symptoms, which makes verifying AI-related symptoms challenging (Hofso et al., 2012). Additionally, pre-therapy symptoms are associated with suboptimal adherence and increased discontinuation (Bender et al., 2014; Kidwell et al., 2014). Measuring symptoms pre-therapy and prospectively aids in assessing changes to symptoms over time. Examining temporal patterns of AI-related symptoms may inform intervention timing as well as identify differences among women's symptom phenotypes.

1.2.8 Symptoms are a Barrier to AI Adherence

Drug-related symptoms are a barrier to adherence to medications for multiple chronic conditions, including HIV/AIDS (Li et al., 2017), tuberculosis (Zegeye et al., 2019), multiple sclerosis (Visser et al., 2020), schizophrenia (Souaiby et al., 2019) and hypertension (Kretchy et al., 2015). In women with breast cancer, symptoms are the leading reason for not adhering to AI regimens, and the symptoms vary in prevalence rates, type, and severity (Aiello Bowles et al., 2012; Bender et al., 2014; Lintermans et al., 2014; Murphy et al., 2012; Sawesi et al., 2014; Wouters et al., 2014). Symptoms are defined as AI-, disease-, and treatment-related symptoms. For example, the symptom experience incorporates self-reported symptoms that may be related to

the AI, to the cancer itself, to the surgery, or to perceived economic hardship. Regardless of the term, symptoms are distressing to patients and are associated with AI nonadherence and discontinuation (Henry et al., 2012; Markopoulos et al., 2015; Moscetti et al., 2015; Neven et al., 2014). Two systematic reviews corroborated the association between symptoms and AI adherence (Murphy et al., 2012; Sawesi et al., 2014). Murphy et al. (2012) distinguished a difference between adherence and discontinuation with prevalence rates of 41–72% and 31–73%, respectively and adherence rates of 50–91% for aromatase inhibitors specifically. They also found that many factors had mixed results (e.g. age, out-of-pocket costs) but symptoms were generally negatively associated with AI adherence (Murphy et al., 2012). Sawesi et al. (2014) found 9 studies that associated symptoms with endocrine therapy adherence, in addition to other factors related to adherence (Sawesi et al., 2014). Of note, neither systematic review was able to conduct a meta-analysis of the factors associated with adherence, in part due to different symptom measures and types of symptoms examined. Unfortunately, this inconsistency has impeded the ability to draw strong conclusions by combining results across studies in a meta-analysis.

As early as 1989, researchers put forth a framework for understanding adherence behavior and methodological issues in adherence research to cancer regimens including effective provider communication and rapport with the provider; the patient's beliefs and attitudes and social climate and norms; the patient's behavioral intentions and supports for and barriers to adherence (Gritz et al., 1989). The authors made suggestions for using biomedical variables, multiple measures of adherence at multiple timepoints, including adherence rates in clinical trials, and using multivariate statistical analysis (Gritz et al., 1989). For the most part, these suggestions were not implemented in subsequent AI adherence and symptom research.

Table 3 summarizes results of studies that have examined relationships between symptoms and adherence. The designs, symptom types, measures, timing, and covariates are sometimes too disparate to elicit a broad conclusion. Some AI-related symptoms are associated with less adherence and discontinuation, such as headaches (Aiello Bowles et al., 2012), depressive and anxiety symptoms (Bender et al., 2014; Brier et al., 2015), and pain (Brier et al., 2017; Henry et al., 2012). However, not all studies found a relationship between increased symptoms and lower AI adherence (Boonstra et al., 2013; Ziller et al., 2009). One study found that adherent participants had fewer symptoms than nonadherent participants at 12 months (Kyvernitakis et al., 2014). Pre-therapy symptoms affect adherence (Bender et al., 2014; Kidwell et al., 2014), and more pretreatment symptoms increased the odds of AI discontinuation (Kidwell et al., 2014). The majority of studies have concluded that there is an association between AI adherence and symptoms. However, few studies have used a pre-therapy assessment and prospective design and incorporating pre-therapy symptoms will aid in assessing temporal changes to symptoms. The substantial variation in design and methodology, including the symptoms examined, measures used, timepoints assessed, and covariates included in statistical analyses have impeded a full understanding of this relationship. Our study will examine adherence and several types of symptoms concurrently and prospectively. We will use symptom and adherence assessments over time including a pre-therapy symptom assessment.

1.2.9 Phenotypic Covariates of Adherence and Symptoms

As summarized in Table 3, clinical and sociodemographic factors have been associated with endocrine therapy adherence: age, marital status, education, comorbid conditions, disease

stage, income, employment, and regimen cost and complexity (Kesmodel et al., 2018; Murphy et al., 2012; Sawesi et al., 2014). Similarly, certain factors are associated with symptoms experienced, including age and education (Aiello Bowles et al., 2012), and comorbid conditions may influence symptoms or adherence (Neugut et al., 2016; Yang et al., 2016). However, these factors have been inconsistently associated, and the direction of the association has varied. For example, one group found that being younger and being older were associated with AI discontinuation (Hershman et al., 2010).

Table 3 Review of Studies Examining Endocrine Therapy Adherence and Symptoms

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Aiello Bowles et al., 2012) US	Total N=538: a. Tamoxifen=348 b. AI =369 Cross-sectional, part of Commonly Used Medications and Breast Cancer Outcomes (COMBO) study mailed survey to those with at least one ET script (pharmacy records) filled between 2002-2008	Self-reported	Discontinuation rate was 18%. Headaches were associated with AI discontinuation (OR=3.20; 95% CI, 1.59-6.45) Of AI discontinuers (n=55), some reasons given (not mutually exclusive): 1. Did not like adverse effects: 66.7% 2. Decreased quality of life (QoL): 43.8% 3. Switched medication: 29.8% <u>Associated with greater adherence:</u> 1. Vaginal dryness (OR 0.42; 95% CI, 0.20-0.86) 2. Hair thinning/loss (OR 0.45; 95% CI 0.21-0.93 3.Hormone or menopause-related symptoms (OR 0.45; 95%CI, 0.24-0.83)	<u>Associated with greater adherence:</u> 1. Taking an AI (OR=0.45; 95%CI, 0.25-0.83) 2. Positive lymph nodes (OR=0.54; 95%CI, 0.31-0.93) 3. Year of diagnosis 2005-08 (OR 0.29; 95%CI, 0.18-0.45) vs 2002-04, when tamoxifen prescriptions were more prevalent
(Atkins & Fallowfield, 2006) UK	N=13 Anastrozole Ancillary study, semi-structured interview	Unintentional: "how often do you forget to take your tablets?" Intentional: "how often do you choose not to take your tablets?"	39 of 131 were not adherent Disliking their treatment (for example, side effects, difficulty swallowing) was associated with less adherence (p=0.001) and was a predictor of less adherence ($\beta = -1.415$, S.E. = 0.421, Exp(β) = 0.243, $p < 0.001$) with age in the model. Women taking anastrozole (n=36): 22 did not adhere, 4 intentionally, 18 unintentionally	<u>Associated with less adherence:</u> younger age (t = 2.483, df = 105.377, p = 0.015, 95% CI: 1.002–8.947)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Bender et al., 2014) US	N=91 Prospective ancillary study within an RCT	Electronic event monitoring (EEM using MEMS™) Microchip in a medication cap that registers date/time of openings	<u>Baseline predictors of less adherence</u>: 1.Depressive symptoms (β −0.8845; $p < 0.01$) 2. Anxiety symptoms (β −0.6682; $0.01 \leq p < 0.05$) 3. Gynecologic Symptoms (β −3.3106; $0.01 \leq p < 0.05$) 4. Weight concerns (β −3.6039; $0.01 \leq p < 0.05$) <u>Predictors of less adherence at 18 months post-ET initiation</u>: 1. Perceived bother from symptoms a. Cognitive symptoms ($p < 0.05$) b. Musculoskeletal pain ($p < 0.05$) c. Weight concerns ($p < 0.01$) d. Gynecologic symptoms ($p < 0.01$)	<u>Associated with less adherence:</u> 1. Time, over 18 months, adherence declined (β = -0.6, p = 0.0009)
(Boonstra et al., 2013) Netherlands	N=57 Patients were grouped by whether they reported arthralgia or not. a. Arthralgia group=42 b. No Arthralgia group=15 Prospective observational	Medication Adherence Report Scale (MARS 5) Self-reported, for this paper, score 0-20, higher scores are more adherent	All patients had symptoms. 67% reported always taking their medication as prescribed (score 0) No significant difference in adherence between the Arthralgia group and the No Arthralgia group.	<u>Associated with higher BMI:</u> 1. the Arthralgia group (vs the No Arthralgia group) There were no other significant differences in patient characteristics between the Arthralgia and No Arthralgia groups.
(Brier et al., 2015) US	N=235 (N=212 were currently taking AI) Wellness After Breast Cancer (WABC) study	Estrone and estradiol levels (to compare with adherence) Morisky Medication Adherence Scale (MMAS8; items 5 and 6 removed) Medication Adherence Scale (MMAS8;items 5 and 6 removed) Visual Analog Scale (VAS) for past month adherence (0-100%) Single question: Have you taken an aromatase inhibitor in the past month? (yes/no)	The MMAS8 total was associated with anxiety and depression. <u>For individual MMAS8 item associations</u>— <u>Anxiety symptoms with</u>: "*cut back or stopped taking your AI without telling your doctor because you felt worse when you took it*" (r_s=0.19, p<0.01) "*when you travel do you sometimes forget to take*" your AI (r_s=0.19, p<0.01). <u>Depressive symptoms with</u>: "*cut back or stopped taking your AI without telling your doctor because you felt worse when you took it*" (r_s=0.31, p<0.01) "*do you sometimes forget to take*" your AI (r_s=0.18, p<0.01) 10% reported they did not take their AI in the last month.	<u>Adjusted for</u>: 1.Race 2.Drug Type

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Brier et al., 2017) US	N=437 Same parent study as Brier et al, 2015 WABC study	Medical chart review: searched for early discontinuation or treatment interruptions (unless they were due toto metastasis or recurrence)	Univariate logistic regression: 1. Joint pain (Brief Pain Inventory) ≥4 associated with nonadherence (OR 1.65 95% CI 1.03-2.67 *p*=0.04) but did not remain significant in multivariate analysis???	Less likely to be nonadherent: 1. >3 years since initiation of ET (OR 0.12 95% CI 0.06-0.26 *p*<.001) remained significant in multivariate analysis (OR 0.13, 95% CI, 0.06-0.26. *p* <.001) More likely to be nonadherent (both univariate and multivariate analyses): 1. high perceived barriers to taking AIs (OR 1.71 95% CI 1.03-2.86 *p*= .04)
(Danilak & Chambers, 2013) Canada	N=346 Retrospective claims data and medical chart of women who initiated ET for breast cancer	Still considered adherent if switched medication	78% filled prescriptions for 2 years Of those who discontinued, 20% were due to side effects according to the chart 9 patients switched due to side effects	More likely to discontinue early (multivariate): 1. No chemotherapy (OR 1.9; 95% CI, 1.0-3.4, *p*=0.04) 2. Clinic follow-up in less than 1 year 3-6 months (OR 2.4; 95% CI, 1.0-5.5, *p*=0.04)
(Farias et al., 2016) US	N=6,863 Retrospective cohort; women who initiated ET within 12 months of primary treatment	PDC=proportion of days covered; insurance claims data	Multivariable quantile regression: switching ET ≥ 2 times associated with lower proportion of days covered (OR 95% CI, 2.3-9.0).	Associated with less adherence: 1. higher out of pocket costs (*p*<0.01) Associated with more adherence: 1. Use of mail order pharmacy (*p*<0.01) 2. Increased age (*p*<0.01) Chemotherapy vs none (*p*<0.01)
(Garreau et al., 2006) US	N=452 Cross-sectional, mailed questionnaire	Self-reported discontinuation	47.5% of women discontinued* their AI due to adverse effects *also referred to this as "switched" in the abstract.	
(Guth et al., 2008) Switzerland	N=325, of which n=287 started ET Retrospective cohort	Medical records data	50/287 switched medications and half (of those 50) switched due to adverse effects 10.8% (31/287) chose to discontinue therapy on their own (most reported adverse effects)	Associated with more adherence: Follow-ups with oncologists (*p*=0.0088)
(Hadji et al., 2013) Germany	tamoxifen N=12,412 anastrozole N=2,796 exemestane N=647 letrozole N=1,657 Retrospective analyses of health database	Discontinuation=90 days without medication within 3 years after initiation	Switched treatment from: tamoxifen 33% anastrozole 20% exemestane 22.9% letrozole 23%	Less likely to discontinue within 3 years: 1. Under gynecologist care (HR 0.44, 95% CI, 0.42-0.46, *p*<0.001) 2. Change of hormone therapy (HR 0.82, 95% CI, 0.77-0.88, *p*<0.001) 3. Have diabetes (HR 0.81, 95% CI, 0.75-0.86, *p*<0.001) 4. Have depression (HR 0.92, 95% CI, 0.87-0.97, *p*=0.002) More likely to discontinue within 3 years: 1. ≤50 years old (HR 1.13, 95% CI, 1.06-1.20, *p*<0.001)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Harrow et al., 2014) Scotland	N=30 Qualitative semi-structured interview 10 women were taking AIs; 4 took tamoxifen then AI	Self-report of med missed dose, temporary stoppage, permanent discontinuation Quotes noted the medication taken	Physician temporarily stopped letrozole due to side effects for 1 of the 30 women 3 of the 30 women stopped taking letrozole due to side effects without medical advice	None reported
(Hashem et al., 2013) US	N=29,967 a. Group A=24,804 No arthralgia prescription b. Group B=5,163 Concurrent arthralgia prescription Retrospective cohort of pharmacy claims data in 1-year period following start of AI	Pharmacy claims data Persistence: refill without exceeding a 60-day gap (on a 90-day prescription) and a 21-day gap (for a 30-day prescription) Discontinuation	Total discontinuation rate was 39.8%. a. Group A discontinuation= 40.9% b. Group B discontinuation= 34.5% (no significant difference between groups) Persistence between groups was different with Group B (with arthralgia prescription) exhibiting better persistence between the following time periods (rates not reported): 1. 0-60 days and 2. 61-300 days (p<0.001)	Age was different between groups (Group A median age=66.7y; Group B median age= 67y; p=.027)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(He et al., 2017) Sweden	N=3,071 a. Continuers n=1607 b. Restarters n=953 c. Nonrestarters n=511 Population based cohort, using registry with a mean 4.49-year follow-up and a survey	Drug registry with prescription fill data for ET and medication for side effects	Baseline predictors of restarting ET, less likely to restart: 1. Less than 50 (results not reported as combined) a. <40 HR 0.67; 95% CI, 0.46-0.97 b. 40-49 HR 0.80; 95% CI, 0.63-1.02 2. 2 or more comorbidities HR 0.53; 95% CI 0.30-0.94) 3. No prior family history HR 0.80; 95%CI, 0.66-0.98) 4. Using hormone therapy 1 year before cancer diagnosis HR 0.75; 95%CI, 0.62-0.91) Better prognosis: 1. HER2 negative HR 0.70; 95% CI 0.51-0.96 2. smaller tumor HR 0.86; 95% CI 0.75-0.99 3. negative lymph nodes HR 0.83; 95%CI, 0.72-0.96 Post diagnosis predictors (adjusted) less likely to restart: 1. Switching HR 0.56; 95% CI 0.45-0.70 2. Discontinuing a. before 1 year (HR 0.67; 95% CI, 0.56-0.80) b. after 3 years of ET (Year 4 HR 0.78; 95% CI, 0.64-0.96 c. Year 5 HR 0.20; 95% CI, 0.14-0.28) 3. Using symptom relieving drugs after discontinuation a. analgesics HR 0.79; 95% CI, 0.66-0.96 b. GI meds HR 0.82; 95% CI, 0.67-0.99 c. 2 or more symptom relieving drugs HR 0.72; 95% CI, 0.58-0.88	Baseline predictors were controlled for in multivariate analysis of post diagnosis predictors (age, prognosis, family history, comorbidities, hormone therapy).
(Henry et al., 2008) US	N=100 Prospective RCT First 100 participants in a trial of 500 (to evaluate pharmacogenomics of AIs—letrozole and exemestane). For this subset, rheumatologic evaluations of musculoskeletal symptoms	Discontinuation	23 of 100 participants discontinued AI therapy (13 of which were due to musculoskeletal symptoms)	No baseline characteristics were associated with development of symptoms
(Henry et al., 2012) US	N=500 Prospective, open-label randomized control trial (exemestane vs. letrozole) for 2 years	Discontinuation	Within the first 2 years, 32.6% of women discontinued their AI due to toxicity (bothersome symptoms) 74.8% (122/163) of those who discontinued due to toxicity did so because of musculoskeletal symptoms; they were 24.4% of the total sample	More likely to discontinue: 1. Younger age (HR 1.4; 95% CI, 1.0-1.9; p=0.04) 2. Taxane-based chemotherapy (HR 1.9; CI, 1.00-3.6, p=.048)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Huiart et al., 2011) UK	N=13,479 Retrospective cohort	Record review medication possession ratio	9.6% of the AI group switched medications	
(Kilic et al., 2011) Switzerland	N=50 who agreed to sequential ET Women with breast cancer identified from database, offered sequential ET switching from tamoxifen (after 2-3 years) to an AI	Nonpersistence by intentional patient action	4% were nonadherent to the new AI medication 18% re-switched to tamoxifen due to side effects 10% re-switched to a different AI due to symptoms	None reported
(Kimmick et al., 2015) US	N=112 Cross-sectional	Morisky Medication Adherence Scale (MMAS8) Beliefs About Medicine Questionnaire	17.7% did not take their medication because they felt worse or had side effects 14.4% stopped taking their medication because it made them feel worse More physical symptoms were related to more intentional nonadherence (r_s=0.26, p=0.007) Poisson regression (controlling for age, race, comorbidity and not including concerns about taking medication: higher score for physical symptoms (Exp(B)=1.51, p=0.03), low self-efficacy for communication with physician (Exp(B)=0.98, p=0.009), and low self-efficacy for taking medication (Exp(B)=0.98, p=0.002) were all predictors of intentional nonadherence	Unintentional nonadherence inversely related to age (r_s=0.23, p=0.02) Intentional nonadherence related to white race (r_s=0.20, p=0.04) and higher comorbidity score (each r_s=0.20, p=0.04) Multivariate analysis controlled for age, race, and comorbidity.
(Kirk & Hudis, 2008) US	N=328 (completed survey) Survey on web site, no forced response questions Breast cancer patients who did not yet start, were currently taking medication, or completed treatment	Self-report	37 of 53 participants named side effects as the reason not to take their medication	
(Kostev et al., 2014) Germany	Gynecologic practices=149 (patients n=3,103) and primary care practices=24 (patients n=321) These practices were grouped by adherence of patients: a.Good compliance practices (98) patients=2,171 b.Poor compliance practices (75) patients=1,253 Retrospective cohort	Discontinuation was a treatment gap of ≥180 days. Practices were determined to be good compliance (≤50% patient dropout) or poor compliance (>50%)	<u>More likely to discontinue early:</u> 1. patients treated in a poor compliance practice (OR=1.57; 95% CI, 1.44-1.70) 2. live in West Germany (OR 1.21; 95% CI, 1.08-1.37) 3. less likely to be seen in a gynecology practice (OR 0.71; 95% CI, 0.62-0.81) 4. osteoporosis (OR 0.81; 95% CI, 0.72-0.90) 5. depression (OR 0.83, 95% CI, 0.76-0.90)	In good compliance practices, more patients stayed on their treatment for 3 years compared with poor compliance practices (69% versus 35%; p<0.01) Discontinuation after 3 years: Good compliance practice patients=19% Poor compliance patients=41% Regression adjusted for age, gender, region, urban residence, gynecological treatment, private/statutory health insurance, osteoporosis, depression, and age, gender of doctor, clinical experience of doctor, and number of patients in practice.

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Kuba et al., 2016) Japan	N=686 Retrospective medical record review	Persistence=continuation of therapy and/or physician's discontinuation of therapy Discontinuation= patient-initiated cessation of therapy	12% (n=79) discontinued on their own; of those, 47% (n=37) stopped due to adverse effects	
(Kyvernitakis et al., 2014) Germany	N=125 a. Compliant group=85 b. Non-compliant group=40 Parent study: COMPliance in Adjuvant treatment of primary breast cancer Study (COMPAS trial; a 3-arm, randomized partially blinded, parallel group comparison over 2 years to improve AI adherence)	Self-report questionnaire medical Medical record review of prescriptions (≥80% was considered adherent)	The Compliant group clarify which reported more anxiety at 12 months than the Non-compliant group or make it a separate(Z= -2.2; *p*=0.028) <u>The Compliant group</u>: 1. Anxiety symptoms decreased from 12-month visit to the 24-month visit (Z=2.19*;* *p*=0.028) 2. Depressive symptoms decreased by 24 months (Z=2.43; *p*= .014) 3. Sleep problems decreased by 24 months (Z=2.1; *p*=.035) <u>The Non-compliant group association</u>: 1. Heart discomfort decreased from 12 to 24 months (Z=2.59; *p*=.009)	None reported
(Lintermans et al., 2014) Belgium	N= 292 about to begin ET a. Tamoxifen group=104 b. AI group=188 (78% letrozole; 21% anastrozole; 1% exemestane) Prospective cohort	How likely is symptom related to ET? Medication Adherence Report Scale (MARS 5) Self-reported adherence with 5 questions	20% of AI group attributed symptoms to ET versus 10% of Tamoxifen group <u>Symptoms that were reported more in AI group</u> (vs Tamoxifen group): 1.loss of sex drive (64% vs 36%) 2.pain during intercourse (34% vs 18%) 3.vaginal dryness (47% vs 27%) Intentional nonadherence mostly due to adverse events Discontinuation of AI in 15% (N=28) of AI group due to adverse events. a. most switched medications b. 4 patients stopped all ET <u>Symptom associated with early discontinuation:</u> 1. Higher baseline average pain (visual analog scale) (*p*=0.0128)	<u>Associated with early discontinuation:</u> 1. BMI quadratic association (*p*=0.0424) 2. Baseline waist-to-hip ratio quadratic association (*p*=0.0325) 3. Age ≤ 55 years old (*p*=0.0125)
(B Makubate et al., 2013) Scotland	N=4,619 Retrospective cohort	Prescribing records Medication Possession Ratio (MPR) Persistence time from first prescription to break of ≥180 days before the 5 years is complete	20% of those started on AI (n=512) switched treatments	More likely to adhere: Older women (*p*<0.0001) Those who started on AI (versus tamoxifen) (*p*=0.001)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Mao et al., 2013) US	N=25,256 online message board posts about AIs Mixed methods study evaluating online message board posts	Posts mentioning discontinuation, side effects, or switching AI	18.2% posts described side effects 12.8% posts discussed discontinuing AI 28.1% posts discussed switching AIs	
(Moy et al., 2006) US, Canada	Minority group: n=352 Minorities included: African American; Hispanic; Asian or Pacific Islander; or Native North American or Native Alaskan. Caucasian group: n=4,708 MA.17 study Secondary analysis of RCT for letrozole/placebo for first 5 years; then5 years of tamoxifen	Pill count Self-report	Minority women taking letrozole experienced: 1. Fewer hot flashes 49% (Caucasian 58%) 2. Less fatigue 29% (Caucasian 39%) 3. Less arthritis 2% (Caucasian 7%) 4. Less diarrhea 3% (Caucasian 7%) 5. More hypertension 9% (Caucasian 5%) 6. SF-36 mental health domain change score better at 6 months (vs Caucasian women) 7. SF-36 bodily pain domain change worse at 12 months (vs Caucasian women) in survival between minority and Caucasian groups Adherence lower in minority group 59.1% versus Caucasian group 68.8% (p<0.0001) Trend for minority group 84.5% versus Caucasian 88% (p=0.07) not missing or losing any pills in the month after randomization	Covariates used in the survival analysis (regression): 1. Age 2. Treatment (letrozole versus placebo) 3. Duration of prior tamoxifen 4. Geographic location 5. Tumor stage 6. Nodal status 7. Prior treatments (surgery) 8. Prior chemotherapy 9. Menopausal status at initiation of tamoxifen (≥50 y)
(Nekhlyudov et al., 2011) US	N=1,408 Retrospective analyses of health plan database of women who initiated ET	Nonpersistence was a gap in prescription refill of 60, 90, or 180 days Medication possession ratio (MPR) >80% was adherence Switching is a change from tamoxifen to AI	79% of women did not have gaps of more than 60 days in their ET 20.3% switched to a different medication Those who switched tended to have fewer gaps in refills	<u>Less persistence:</u> Older women- less likely to persist Time- over time persistence decreases Women in lower income neighborhoods have less persistence
(Robinson et al., 2018) New Zealand	N=674 a. AI= 254 b. Tamoxifen=412 Prospective. Christchurch Breast Cancer Patient Register June 2009-2013		Year 1 90% adherent, Year 2 84% adherent Year 3 81% adherent Year 4 76% adherent Year 4.5 71% adherent Year 5 50% adherent Symptoms were the main reason for discontinuation in 20% of the entire cohort (674). Participants listed their most significant event that led to discontinuation. <u>Arthralgia (p<.01) and decreased bone mineral density (p<.01)</u> were more frequently associated with discontinuation of AIs than with tamoxifen.	

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Schover et al., 2014) US	N=129 a. Group 1 adherent=109 b. Group 2 nonadherent=20 Cross-sectional for those receiving AI 18-24 months	Merck Adherence Estimator Did participant ever fill the prescription? Did participant discontinue the medication? How many days did participant take her AI in the previous 2 weeks?	15.5% were categorized nonadherent by either not filling, discontinuing AI, or taking 7 or less doses in the past 2 weeks (less than 50% adherence) No significant difference on symptoms between groups though adherent women reported more dyspareunia (p=0.0544) Of sexually active women (N=67), 12% switched to AI or tamoxifen, and 1% discontinued ET because of symptoms	<u>Not significant</u>: 1. Age 2. Race 3. Marital status
(Sedjo & Devine, 2011) US	N=13,593 Retrospective cohort using claims database	Medication possession ratio (MPR) Adherent- 80% or more	<u>More likely not to adhere:</u> 1. Initial claim for letrozole (25% more likely not to adhere) and exemestane (66% more likely not to adhere) 2. Women who switched ET medication (adjusted OR 1.37, 95% CI, 1.19-1.59) 3. Those with depressive symptoms (adjusted OR 1.31; CI, 1.19-1.43)	<u>More likely to be nonadherent:</u> 1. Younger age (p<0.01) 2. Out of pocket costs ≥$30 versus<$10 (adjusted OR 2.07, 95% CI, 1.80-2.37) 3. More comorbidities (adjusted OR 1.90; CI, 1.62-2.12) Using a mail order pharmacy reduced nonadherence by 30%
(Simon et al., 2014) Canada	N=161 Qualitative interview of women from one physician practice who had taken ET in the previous 10 years	Questions were asked regarding adherence Prescription copies were in the medical record	For participants with <80% adherence, side effects (n=5) and lack of conviction (n=3) were the most frequent reasons to not adhere.	In women with <80% adherence the following was associated with less adherence: Menopause HER2-neu positive Postop chemotherapy Axillary dissection Hormone replacement therapy
(Stanton et al., 2014) US	N=1,465 Prospective, 2-3 weeks from Army of Women registry, women currently and/or past year taking ET	Modified Morisky Medication Adherence Scale using Likert responses, removing one item and adding 2 items Nonpersistence=breast cancer diagnosis in past 5 years had taken ET in past year but was not currently taking ET	49% switched ET (n=675) Of those, 48% was due to side effects (n=326)	t-test between current users and nonpersisters associated with adherence: more years since diagnosis (p<0.001; 95% CI, 1.36-2.02) fewer depressive symptoms (p<0.001; 95% CI, -2.99 to -1.21) better quality relationship with oncologist (p<0.001; 95% CI, 3.75-7.46) less general physical symptoms (p=0.002; 95% CI, -4.20 to -0.97) fewer negative emotions toward ET (p<0.001; 95% CI, -3.52 to -2.09) more positive emotions toward ET (p<0.001; 95% CI, 2.24-3.35)

Author Year Country	Sample Design	Adherence Measure	Results: Relationship between symptoms and adherence	Covariates
(Taketani et al., 2014) Japan	N= 128 survived for 5 years N=116 (followed for 5 years and completed ET treatment) N=69 SERM group N=33 AI group N=14 switched Retrospective observational	Medical chart review	12 patients (9.4%) discontinued ET; 5 of those were due to side effects. 9.1% (N=3) of AI group (2.6% of total) switched to tamoxifen due to MS pain and 15.9% (N=11) of the tamoxifen group switched to AIs after menopause.	
(Trabulsi et al., 2014) Canada	N=4,715 Historical prospective cohort using provincial health insurance agency data Examined 5-year adherence to endocrine therapy (includes tamoxifen, 94.74% of sample)	Medication Possession Ratio: proportion of days, doses dispensed/dosing period Discontinuation: 60 consecutive days without a claim. Re-initiation: a claim after discontinuation	Switch in first year of treatment decreased MPR by 5.3% (p=0.003) tamoxifen had a lower MPR compared with anastrozole (6%; p=0.002) 34% discontinued ET; 60.9% of those did not resume ET 24.96% switched ET	More prescriptions at baseline improved MPR (0.06%/prescription; p<0.0001) Each new medicine decreased MPR by 0.3% (p=0.0001) Baseline antidepressant use decreased MPR by 4.7% (p=0.003) Women with ductal carcinoma had lower MPR (6.5%; p<0.0002) More hospitalizations decreased MPR (0.73%/hospitalization; p=0.01)
(van Herk-Sukel et al., 2010) Netherlands	N=1725 n= 274 on aromatase inhibitors all from PHARMO-ECR registry Retrospective cohort	Discontinuation Switching Based on refill of tamoxifen or aromatase inhibitor	26% of those on tamoxifen switched to an AI	
(Wigertz et al., 2012) Sweden	N=1741 Retrospective analyses of database/registry	Adherence=80% or more coverage with medication (medication possession ratio MPR) Discontinuation Both followed through pharmacy dispense data	12% discontinued treatment early 31% were nonadherent in 3 years' time Those who switched medications were less likely to be adherent (OR 0.7, 95% CI, 0.5-0.9)	<u>Greater adherence associated with:</u> Younger age at diagnosis (OR 1.4, 95% CI, 1.0-1.9) Larger tumor <u>Less adherence:</u> Born outside a Nordic country (OR 0.6, 95% CI, 0.4-0.9) Not being married (OR 0.7, 95% CI, 0.6-0.9)
(Wouters et al., 2014) Netherlands	N=241 Cross-sectional, online or in person survey and refill claims data	Medication Possession Ratio derived from refill data Adherence Rating Scale: (MARS 5) pooled with Morisky Medication Adherence Scale (MMAS8)	Greater number of symptoms are associated with intentional nonadherence (OR, 1.2; 95% CI, 1.05-1.4)	<u>Predictors of unintentional nonadherence:</u> 1. Age (OR, 0.94; 95% CI, 0.90-0.99) 2. Treatment for recurrent breast cancer (OR, 0.2; 95% CI, 0.1-0.9) 3. Perceived self-efficacy for taking med (OR, 0.5; 95% CI, 0.4-0.7) <u>Intentional nonadherence predictor</u>: 1. Perceived self-efficacy for learning about ET (OR, 0.6; 95% CI, 0.4-0.96)
(Ziller et al., 2009) Germany	N=100 Postmenopausal women treated for 1-2 years with tamoxifen or AI Cohort: survey and retrospective review	Self-report and medical record review medication possession ratio (MPR)	No significant relationship was found between adherence and side effects	

1.2.10 Inter-individual AI-related Symptom Variability Characterization

The nature of inter-individual variability in symptoms among women taking AIs has not been fully characterized. The etiology of symptoms experienced during AI therapy may, in part, have biological underpinnings, yet little is known about factors in AI (anastrozole, letrozole, exemestane) absorption, distribution, metabolism, and elimination (ADME) pathways and resulting symptoms (Hamadeh et al., 2018). Variations in ADME pathways may, in part, explain AI symptoms variance, as well as discordance of drug plasma and estradiol levels (Borrie & Kim, 2017; Daniel L Hertz et al., 2017). Some evidence supports this theory, but few studies have examined genes involved in anastrozole ADME (Artigalas et al., 2015; Baatjes et al., 2017). Research on other drugs shows that the high degree of variability in symptom frequency, type, and severity results from numerous intrinsic or extrinsic factors which exert influence on ADME, and this may also be the case for the symptoms women experience when taking AIs (Wilkinson, 2005). Our study plans to examine the potential role of ADME factors in patterns of symptoms and adherence.

1.2.10.1 Intrinsic Factors

Potential intrinsic factors identified as contributors to inter-individual variability in symptoms include aging, sex, and genotype. Variability in drug response associated with aging centers on gastrointestinal absorption, distribution, and elimination. Xenobiotic absorption changes with advanced age due to changes in gastric pH, motility, surface area, and gut microbial diversity (Clarke et al., 2019; Thummel & Lin, 2014). Distribution is affected by body fat, total body water, and xenobiotic transporters (albumin and alpha-1-acid glycoprotein) (Bteich, 2019). Aging affects elimination when kidney function decreases and fatty liver incidence increases

(Chen & Madak-Erdogan, 2018; Pottel et al., 2017). Our study sample is mostly older, a population that is usually not well-studied in clinical trials.

Research suggests sex differences play a role in drug ADME. Women consistently experience more symptoms from xenobiotic ingestion (de Vries et al., 2019). Aside from sex differences in body weight and composition, hormone levels, and tissue expression of P450, little is known about how sex differences affect xenobiotic ADME and the reasons women experience symptoms more frequently and with greater severity (Franconi & Campesi, 2014). Conflicting results regarding sex differences for drug ADME among the P450 system genes are often due to inadequate sample size and confounding variables. Thus, more study of this factor is warranted. However, results suggest that sex differences for the P450 system gene expression were either increased or decreased based on the gene and the tissue (Thummel & Lin, 2014). For example, *CYP3A4* tends to be expressed more in liver tissue in women than in men, though not significantly (Parkinson et al., 2004). Aside from sex differences, genotype also exerts an influence on drug ADME and the subsequent drug response phenotype. Our study sample is exclusively female and will contribute to ADME-symptom research in women.

Genotype is a significant intrinsic factor in drug ADME, and it may play a role in the inter-individual variability in symptoms in women taking AIs. Genes involved in drug ADME may be related to metabolism, transport, or the drug target. Examples of metabolism genes are those in the P450 system (*CYPs*). Transporter genes may be involved with absorption, distribution, or elimination (*ABCs, SLCs)* (Nigam, 2015; Rosenthal et al., 2019). Drug target genes vary depending on the drug, and *CYP19A1* (aromatase) is the target for anastrozole.

Pharmacogenetic (PGx) research examines how genotype affects drug ADME and subsequent response and incorporates pharmacokinetics, the body's effect on the drug (ADME),

and pharmacodynamics, the drug's effect on the body (efficacy, symptoms). PGx research has led to changes in clinical practice recommendations for treatments in cardiology, psychiatry, and oncology. For example, a loss of function for the *CYP2C19* gene results in a poor metabolizer phenotype for the antiplatelet agent clopidogrel and little to no efficacy of the drug (Tuteja & Limdi, 2016). Loss of function for *CYP2D6* is associated with a poor metabolizer phenotype for paroxetine, resulting in an increase in symptoms (Hicks et al., 2015). And loss of function for the *DPYD* gene with fluoropyrimidines is associated with more severe toxicities (Amstutz et al., 2018). However, not all drugs are good candidates for PGx evaluation.

1.2.11 Anastrozole as a Focus of PGx ADME Research

For a drug to be considered a good candidate for PGx ADME research, two characteristics should be considered: 1) a narrow therapeutic window (NTW) and 2) a single gene driving the ADME process (Brazeau, 2015). A therapeutic window is considered narrow when the dosage between efficacy and adverse reactions is small (Blix et al., 2010), which makes finding a PGx target clinically meaningful, even critical. The definition of NTW assumes that the drug is consistently taken on time with the prescribed dose; and expanding the definition to include dose timing and persistence may be advantageous in cases where not taking the drug would change the nature of the drug target. For example, patients with HIV must consistently take their drug regimen within a very narrow time window for efficacy and for prevention of HIV mutations which result in drug resistance (Vrijens & Urquhart, 2005). A known characteristic of cancer cells is their high mutation rate and their ability to become resistant to treatment through several mechanisms (Hanahan & Weinberg, 2000). Drug resistance in cancer is a major problem for any treatment. For endocrine therapy, breast cancer may become resistant to both selective estrogen receptor

modulators (SERMs) and AIs with treatment failure between 20-40% (Liu et al., 2019; Ma et al., 2015). Arguably, if women do not adhere to their full AI treatment as prescribed, they risk creating an environment for cancer cells to mutate and become resistant, which will set the stage for recurrence and progression. Therefore, it is plausible that the window for efficacy narrows when the treatment targets (cancer cells) are given an opportunity to mutate and become resistant.

A drug with one gene driving ADME makes a PGx target easier to discover and simplifies implementation of clinical treatment decisions. AI PGx is a relatively new area of research which has not been fully explored, and a single gene driving anastrozole's ADME has not been identified (Sini et al., 2017). The aromatase gene (*CYP19A1*) biological pathway is the target for AIs, which inhibit the enzyme production in all tissues (Figure 1). *CYP19A1* inhibition prevents conversion of androgens (androstenedione, testosterone) to estrogens (estrone, estradiol). In postmenopausal women (who no longer produce estrogen in the ovaries), *CYP19A1* inhibition suppresses/eliminates the body's source of estrogen, thereby preventing HR+ tumor proliferation in the breast. In the process, estrogen production throughout the body is suppressed in all bodily tissues, and this suppression is associated with numerous symptoms. Given the propensity of AIs to be associated with a myriad of bothersome symptoms with a high inter-individual variability, AIs make a good PGx target.

Mixed results are found in studies attempting to find relationships among drug or hormone levels, genotype, and symptoms. *CYP2A6*, an AI ADME gene, was associated with variations in letrozole drug levels in blood. Median letrozole concentrations were 81.2 ng/ml for normal metabolizers, 112.4 ng/ml for intermediate metabolizers, and 152.1 ng/ml for slow metabolizers (Desta et al., 2011). A contrasting study indicated that women reporting improvement in symptoms after switching AIs had no significant change in estradiol levels (Kadakia et al., 2017; Kadakia et

al., 2016). This is a contradiction in results as one might expect drug levels to affect estradiol levels and subsequently impact symptoms, but this outcome may indicate that AIs have similar PGx genes. Another gene, estrogen receptor 1, *ESR1,* is in the aromatase inhibitor pathway and was associated with symptoms and exemestane discontinuation, but estradiol levels were not assessed (Henry et al., 2013).

For anastrozole, an *ABCB1* single nucleotide variant (SNV) was associated with highly variable anastrozole plasma variations, and 2 SNVs (from *ABCB1*; *CYP19A1*) were associated with decreased risk for arthralgia symptoms (Gervasini et al., 2017). A systematic review for *CYP19A1* SNVs associated with AIs did not find definitive results for ADME, but suggested that the rs4646 variant may be protective for time to progression, indicating that outcomes can be affected by ADME pathways (Artigalas et al., 2015). A recent review reported that there were no clear, strong associations for PGx genes and anastrozole to date, but this area of research was worth pursuing (Sini et al., 2017). Possible ADME genes for anastrozole include *UGT1A4* and *CYP3A4/5/7* (Daniel L Hertz et al., 2017; Kamdem et al., 2010). These reviews suggest that ADME genes for anastrozole should be identified and their role in symptoms experienced should be characterized.

1.2.11.1 Extrinsic Factors

Possible extrinsic factors affecting drug ADME include environment (smoking, etc.), diet (foods, alcohol, etc.), and other drugs (including supplements). These external factors may influence drug ADME (Lynch & Price, 2007) and may be inducers or inhibitors. An inducer is a drug/substance that stimulates production of ADME gene products, and thereby increases the rate of drug ADME and results in increased production of ADME gene products. An inhibitor is a drug/substance in competition for the same receptor site, and thereby decreases production of

ADME gene products. A familiar extrinsic factor is dietary—grapefruit juice. *CYP3A* is inhibited for up to 48 hours after drinking a glass of grapefruit juice, and avoidance is recommended in patients taking *CYP3A*-metabolized drugs, such as felodipine or cyclosporine (Wilkinson, 2005). Another familiar extrinsic factor is co-ingestion of drugs or supplements that potentiate/inhibit drug ADME. For example, adding ritonavir to HIV treatments will inhibit *CYP3A* thereby increasing drug plasma levels (Wilkinson, 2005). Therefore, it is important to account for current medication regimens in analyses of ADME genes. We will assess the role of baseline (pre-anastrozole) medication regimens in anastrozole ADME. Our preliminary study 3 found some relationships between symptoms and baseline (pre-anastrozole) medication regimen categories.

1.2.11.1.1 Prodrugs or Active Drugs

The type of drug will make a difference in the ADME process. Prodrugs must be activated in the body by an enzyme produced by an ADME gene. When one or both ADME gene alleles have a gain of function (more enzyme activity), there is increased metabolism, and the typical dose of drug results in an increased drug exposure (see Figure 2, line 2). A possible remedy to reduce drug overexposure is to decrease the drug dose. When one allele has a loss of function (little enzyme activity), the body metabolizes the drug to a lesser degree, resulting in little drug exposure. It may be possible to increase the dosage to improve drug exposure. However, when both alleles have loss of function (no enzyme activity), the only option is to prescribe a different drug (see Figure 2, line 4).

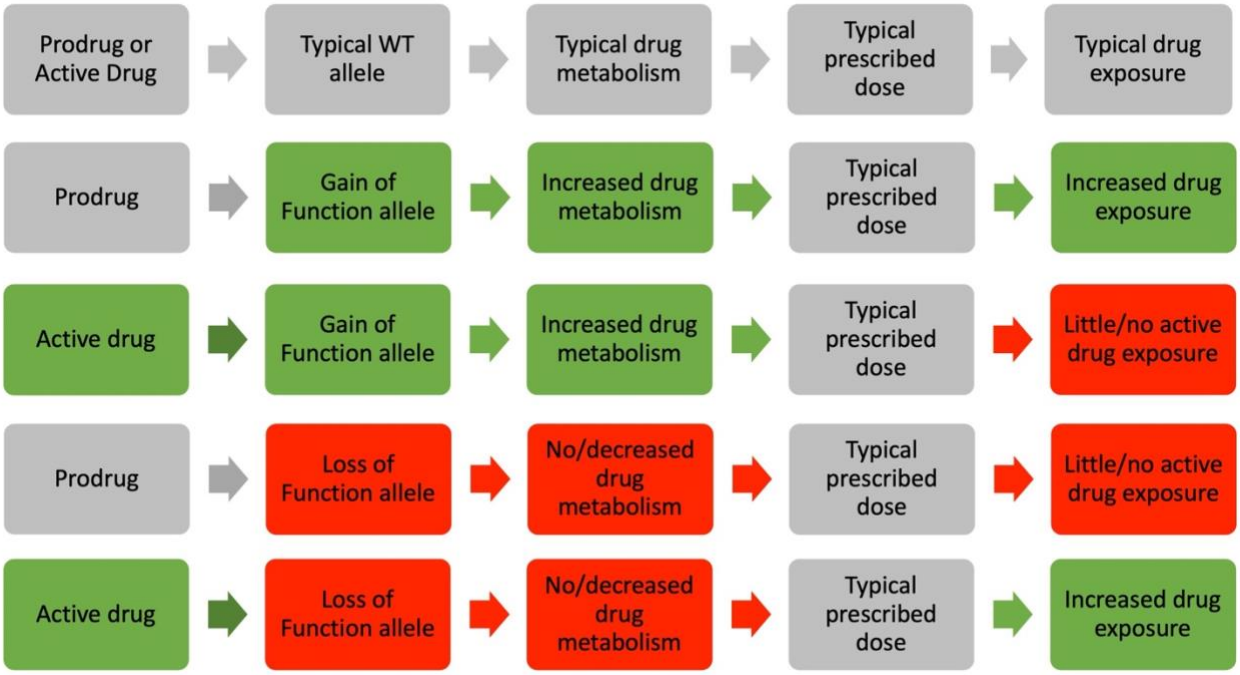


Figure 2 Process of PGx drug metabolism genes with active and prodrugs

Active drugs, like anastrozole, are ingested in their active form and do not require the prodrug activation step. In the case of active drugs, the enzymes metabolize the drug for elimination from the body. When one or both alleles have a gain of function (more enzyme

activity), there is an increased metabolism, and the typical dose of drug results in little or no active drug exposure (see Figure 2, line 3). When one or both alleles have a loss of function (little or no enzyme activity), the body metabolizes the drug to a lesser degree, resulting in increased drug exposure (Figure 2, line 5). This is due to the inability to break down the active drug into a metabolite that can be eliminated. One possible remedy for this situation is to decrease the prescribed dose. Since anastrozole is an active drug, and its metabolites are inactive with respect to aromatase inhibition, (*Anastrozole*, 2021; Plourde et al., 1995; Plourde et al., 1994) we expect a loss of gene function would produce prolonged exposure and a subsequent increase in symptoms.

1.2.12 The Proposed Study Will Address Several Gaps in Current Knowledge

To date, the temporal patterns of AI adherence and symptoms have not been fully characterized, nor has their relationship to each other over time been examined. Little information exists on adherence post-AI initiation at the daily level. In addition, the role of genotypic and phenotypic factors to AI adherence and symptoms is not clear. The dissertation study will use a precision health care approach to address several gaps by 1) phenotypically classifying temporal patterns of symptoms and adherence over the first 18 months of AI therapy; 2) examining the relationship between symptom and adherence patterns; and 3) exploring genotypic and phenotypic factors associated with those classifications. Examining these patterns will identify timing and patterns for future interventions and may provide insight on why these variations exist as well as features associated with membership in the subgroups. These features may be patient and/or treatment characteristics of subgroup membership (demographic or clinical phenotypes) or ADME factors. Genotype and concurrent medication regimens may affect adherence and/or symptoms directly or via moderation. We acknowledge the complex, cyclical nature of the adherence-

symptom relationship and the role of phenotypic and genotypic covariates, which will be used to describe subgroup membership characteristics among women.

This dissertation research will lay the groundwork to shift the AI therapy paradigm from a symptom-reactive to an adherence-proactive approach by 1) identifying critical timing to conduct future symptom management and adherence interventions; 2) identifying relationships between symptom and adherence patterns; and 3) exploring genotypic and phenotypic factors associated with the patterns. Therefore, the aims for this dissertation study align with the National Cancer Institute's mission by advancing scientific knowledge of factors that interfere with treatment and helping women to live longer lives with a better quality of life by expanding personalized health care strategies to AI therapy.

1.3 Preliminary Analyses

In this section, we discuss preliminary study results that support the aims of this dissertation project.

1.3.1 Study 1

Literature supports the idea that biological mechanisms have a role in symptom development. In a review and pathway analysis (McCall et al., 2018), our team examined current literature for omics-based approaches to pain, cognitive impairment, sleep disruption, gastrointestinal distress, and fatigue without regard for disease state. Twenty-seven genes (shown in Appendix C, Table 1) were associated with more than one of the symptoms. The genes were

associated with immune, inflammatory, and/or cell signaling canonical pathways. Notably, two of the genes associated with symptoms are also ADME genes:

1) *ABCB1,* a drug efflux gene (*GeneCards – the human gene database: ABCB1*, 2020; Stelzer et al., 2016), is involved in drug ADME (and drug resistance) and was associated with cognitive impairment, gastrointestinal distress, and pain in the review. This drug absorption gene is associated with multidrug resistance, making it a logical candidate for this study (Gervasini et al., 2017).

2) *ESR1,* the estrogen receptor 1 gene is a transcription factor gene with a role in sexual development, bone health, cancer, and cardiovascular health (*GeneCards – the human gene database: ESR1*, 2020; Stelzer et al., 2016), and it was associated with cognitive impairment and pain in the review. Taking into consideration sex differences found in xenobiotic symptoms (de Vries et al., 2019), this gene will be a compelling candidate gene for this study.

The review illustrated the proof of concept for the proposed dissertation study that common biological underpinnings of symptoms experienced without regard for a specific disease, although it was limited by previously-conducted research. It suggests that common mechanisms may occur across disease processes and symptoms. The list of genes associated with symptoms in Appendix C Table 1 presents good candidates for genetic evaluation of more than one symptom. Given that *ABCB1* and *ESR1* were associated with more than one type of symptom and one of their roles is drug ADME, we may examine these genes in the dissertation study. Study 2 is a preliminary examination of *ESR1*.

1.3.2 Study 2

In this preliminary study, we conducted an exploratory analysis of *ESR1* and progesterone receptor *(PGR)* polymorphisms and self-reported symptoms, measured with the total and subscale scores from the Breast Cancer Prevention Trial checklist (BCPT) as predictors of adherence at 6- and 12-months post-initiation of anastrozole in the same sample of women with early-stage breast cancer used for Aim 3 (n=97), the exploration of genes as predictors of trajectory group membership. We hypothesized that, due to *ESR1*'s location in the estrogen pathway (Figure 1), *ESR1*'s association with more than one symptom (McCall et al., 2018), and sex differences in xenobiotic symptoms (de Vries et al., 2019), *ESR1* and *PGR* polymorphisms will have an association with anastrozole adherence, symptoms experienced, and commonly associated covariates.

The women in this sample were mostly Caucasian (97.9%), well-educated (mean 15.3 years), diagnosed with Stage 1 breast cancer (73.2%), and were age 49 to 74 years (mean 60.7 years). Using Mann Whitney *U* testing, adherence at 6 months trended toward association with BCPT symptom totals at 6 months but was significantly associated at 12 months (p=.013). Subscales that trended or reached significance were cognitive and gastrointestinal subscale scores at all 3 timepoints (cognitive pre-therapy p=.055, 6-month p=.011, and 12-month p=.005; gastrointestinal pre-therapy p=.050, 6-month p=.074, 12-month p=.000); weight concerns at 6 and 12 months (p=.000 and p=.026, respectively); and gynecological at 12 months (p=.024). Adherence at 12 months was associated with cognitive subscale scores at 6 and 12 months (p=.011 and p=.009, respectively) and the weight concerns subscale at 6 months (p=.046) (results shown in Table 4.

Table 4 BCPT Symptoms by Anastrozole Adherence at 6 and 12 Months

Adherence at 6-months							
BCPT Score or Subscale	**Time**	***U***	**Adherent Group A**		**Nonadherent Group NonA**		**p-value**
			Mean	**Median**	**Mean**	**Median**	
Total	Pre-AI	555.00	19.55	17.00	26.80	23.00	.138
	6-month	465.50	21.92	18.50	29.04	25.50	.066
	12-month	**324.00**	**21.27**	**18.44**	**31.43**	**27.00**	**.013**
Cognitive	Pre-AI	483.50	1.85	2.00	3.22	3.00	.055
	6-month	**389.00**	**2.03**	**1.00**	**3.39**	**3.00**	**.011**
	12-month	**281.50**	**1.79**	**1.00**	**3.62**	**3.00**	**.005**
Gastrointestinal	Pre-AI	551.00	.35	.00	.89	.00	.050
	6-month	527.00	.26	.00	.61	.00	.074
	12-month	**331.50**	**.16**	**.00**	**.94**	**.00**	**.000**
Weight Concerns	Pre-AI	663.00	.44	.00	.89	.00	.536
	6-month	**368.50**	**.21**	**.00**	**.82**	**1.00**	**.000**
	12-month	**407.00**	**.16**	**.00**	**.76**	**.00**	**.026**
Gynecological	Pre-AI	662.00	.37	.00	.42	.00	.548
	6-month	634.00	.26	.00	.56	.00	.839
	12-month	**395.50**	**.22**	**.00**	**.76**	**.00**	**.024**
Adherence at 12-months							
Cognitive	Pre-AI	649.50	1.83	1.00	2.27	2.00	.295
	6-month	**449.00**	**1.97**	**1.00**	**3.00**	**3.00**	**.011**
	12-month	**370.50**	**1.73**	**1.00**	**3.00**	**3.00**	**.009**
Weight Concerns	Pre-AI	704.00	.49	.00	.26	.00	.263
	6-month	**572.50**	**.22**	**.00**	**.57**	**.00**	**.046**
	12-month	614.50	.25	.00	.43	.00	.805

Note:Pre-AI = pre-therapy; A= Adherent group= ≥80% adherence; NonA= Not adherent group= <80% adherence
Bold= p<.05

These bivariate analyses suggest that women with symptoms are less adherent, and they prompt more questions. How does experiencing more symptoms for the NonA group relate (or not relate) to taking the AI? Are women in the NonA group more sensitive to symptoms in general or from an AI specifically?

Common covariates for adherence, such as age, educational level, medication complexity, cancer stage, and receipt of chemotherapy were not associated with anastrozole adherence. However, being married was associated with being adherent (adherence of at least 80%) at 6 months (OR 2.857; 95% CI 1.018-8.019; p=.041) but not at 12 months (OR 1.885; 95% CI .711-4.995; p=.199). Having chemotherapy was associated with higher BCPT symptom scores at pre-therapy for the total score and cognitive, musculoskeletal, vasomotor, gastrointestinal, dyspareunia, and weight concerns subscales. At 6- and 12-month timepoints, only the cognitive subscale was significantly associated with having chemotherapy, with more cognitive symptoms

for women who received chemotherapy. Therefore, potentially, women who are married have some type of support for better adherence and women who have had chemotherapy initially experience more symptoms that wane over time.

Several *ESR1* SNVs were associated with symptom scores. However, it should be noted that *ESR1* has a high level of linkage disequilibrium (LD), in which many SNVs are highly correlated. Results of the Mann Whitney U testing for BCPT symptom scores (total and subscales) that were beneath the screening cut point of p<.1 are shown in Table 5. BCPT symptom subscales reached statistical significance (p<.05) for each of the eight subscales and/or the total score at one or more timepoints for at least one SNV.

Several *ESR1* SNVs were explored for their association with adherence and met the p<.1 cut point for further exploration, as shown in Table 6. One SNV reached significance p<.05 for 12-month adherence (rs3778099) with TT genotype having 4 times the odds of being adherent at 12 months than the CT (OR 4.156, 95% CI 1.223-14.125; p=.036, Fisher's Exact).

Table 5 BCPT Symptom Subscales by *ESR1* SNVs 2-group Mann Whitney U (p<.1)

SNV/ genotype Group 1 v. Group 2	BCPT Subscale	Time	*U*	Group 1		Group 2		p-value
				Mean	Median	Mean	Median	
rs851967 G v. A/GA	**Dyspareunia**	**Pre-AI**	**881.50**	**1.49**	**1.00**	**.73**	**.00**	**.019**
	Dyspareunia	12-month	578.50	1.74	1.00	1.15	.00	.055
rs851971 G v. A/AG	**Dyspareunia**	**Pre-AI**	**877.50**	**1.36**	**1.00**	**.73**	**.00**	**.038**
rs851998 C v. T/TC	**Dyspareunia**	**Pre-AI**	**881.50**	**1.49**	**1.00**	**.73**	**.00**	**.019**
	Dyspareunia	12-month	578.50	1.74	1.00	1.15	.00	.055
rs1062577 T v. A/AT	Total	Pre-AI	381.50	19.88	17.00	27.00	20.00	.090
	Vasomotor	Pre-AI	369.00	1.64	1.00	3.31	3.00	.057
	Dyspareunia	6-month	353.50	1.27	.00	2.46	2.00	.062
rs1801132 C v. G/CG	Dyspareunia	Pre-AI	890.00	1.28	1.00	.84	.00	.072
rs1884051 A v. G/GA	**Bladder**	**12-month**	**570.00**	**1.24**	**.00**	**1.29**	**1.00**	**.048**
	Weight concerns	12-month	627.00	.15	.00	.45	.00	.083
rs2046210 C v. T/TC	**Dyspareunia**	**12-month**	**487.00**	**.97**	**.00**	**1.67**	**1.00**	**.031**
	Bladder	6-month	762.50	.68	.00	1.14	.00	.073
rs2077647 G v. A/GA	Vasomotor	Pre-AI	621.50	2.27	2.00	1.77	1.00	.095
	Gastrointestinal	**6-month**	**596.50**	**.50**	**.00**	**.28**	**.00**	**.027**
	Gastrointestinal	**12-month**	**445.50**	**.68**	**.00**	**.21**	**.00**	**.018**
	Gynecologic	12-month	471.00	.68	.00	.24	.00	.076
rs2228480 G v. A/GA	**Vasomotor**	**12-month**	**542.00**	**2.96**	**3.00**	**2.17**	**1.00**	**.026**
	Bladder	Pre-AI	830.50	.62	.00	1.15	1.00	.068
	Weight concerns	12-month	650.50	.42	.00	.10	.00	.097
rs2234693 C v. T/TC	**Vasomotor**	**12-month**	**312.00**	**3.94**	**3.00**	**2.47**	**1.00**	**.014**
	Gastrointestinal	**6-month**	**467.00**	**.63**	**.00**	**.26**	**.00**	**.008**
	Gastrointestinal	**12-month**	**375.00**	**.59**	**.00**	**.27**	**.00**	**.016**
	Dyspareunia	**Pre-AI**	**493.00**	**.53**	**.00**	**1.21**	**.50**	**.039**
rs2347867 A v. G/GA	Total	12-month	574.00	27.39	22.00	19.29	17.50	.068
rs2744677 A v. C/CA	Dyspareunia	Pre-AI	846.00	.74	.00	1.52	.50	.076
	Dyspareunia	**6-month**	**659.50**	**.86**	**.00**	**2.03**	**1.00**	**.012**
	Bladder	12-month	596.00	1.29	1.00	.58	.00	.075
rs2813543 G v. A/AG	**Weight concerns**	**12-month**	**535.00**	**.16**	**.00**	**.59**	**.00**	**.019**
rs2813544 A v. G/AG	Gastrointestinal	6-month	797.00	.44	.00	.15	.00	.078
rs2941740 T v. C/TC	**Total**	**6-month**	**667.00**	**18.75**	**17.00**	**25.46**	**22.50**	**.030**
	Musculoskeletal	6-month	699.50	4.59	4.00	6.09	6.00	.057
	Weight concerns	6-month	771.50	.14	.00	.40	.00	.091
rs3020314 T v. C/CT	**Bladder**	**12-month**	**505.00**	**1.29**	**1.00**	**.85**	**.00**	**.025**
rs488133 C v. T/TC	Cognitive	Pre-AI	815.00	20.88	17.00	20.69	20.00	.075
	Cognitive	6-month	732.00	22.95	19.50	23.91	21.00	.091
	Vasomotor	**Pre-AI**	**796.00**	**2.32**	**2.00**	**1.44**	**.50**	**.034**
	Gastrointestinal	**6-month**	**796.00**	**.52**	**.00**	**.17**	**.00**	**.039**
rs6557171 C v. T/CT	**Total**	**12-month**	**644.00**	**27.20**	**22.00**	**19.27**	**17.50**	**.048**
rs7761846 T v. C/CT	Musculoskeletal	6-month	235.50	5.89	5.00	3.56	2.00	.089
	Bladder	6-month	237.00	1.08	.00	.11	.00	.057
	Bladder	**12-month**	**191.00**	**1.16**	**1.00**	**.22**	**.00**	**.037**
	Weight concerns	6-month	259.50	.27	.00	.67	.00	.060
	Gynecological	6-month	270.00	.40	.00	.00	.00	.093
	Gynecological	12-month	234.00	.39	.00	.00	.00	.088

	Total	12-month	590.50	18.83	18.00	28.30	22.50	.071
	Musculoskeletal	12-month	591.50	4.67	3.00	6.25	5.00	.071
rs7767143	**Gastrointestinal**	**6-month**	**755.50**	**.16**	**.00**	**.58**	**.00**	**.010**
A v. G/AG	**Gastrointestinal**	**12-month**	**611.50**	**.16**	**.00**	**.53**	**.00**	**.019**
	Weight concerns	**Pre-AI**	**850.00**	**.33**	**.00**	**.82**	**.00**	**.037**
	Gynecological	12-month	647.50	.19	.00	.53	.00	.089
	Vasomotor	Pre-AI	581.50	2.43	2.00	1.72	1.00	.045
rs827421	Gastrointestinal	6-month	605.50	.48	.00	.29	.00	.050
C v. T/TC	**Gastrointestinal**	**12 month**	**454.50**	**.65**	**.00**	**.22**	**.00**	**.036**
	Gynecological	12 month	446.50	.70	.00	.24	.00	.042
rs851982	**Total**	**6-month**	**635.50**	**18.61**	**16.00**	**25.20**	**22.00**	**.025**
T v. C/CT	Cognitive	6-month	660.50	1.62	1.00	2.50	2.50	.060
	Musculoskeletal	**6-month**	**627.50**	**4.28**	**4.00**	**6.18**	**6.00**	**.020**
rs9322331 C v. T/TC	**Gastrointestinal**	**Pre-AI**	**694.50**	**.83**	**.00**	**.23**	**.00**	**.005**
rs9340799	Cognitive	Pre-AI	722.50	2.57	3.00	1.98	1.00	.094
A v. G/GA	**Gastrointestinal**	**Pre-AI**	**629.50**	**.97**	**.00**	**.23**	**.00**	**.001**
	Gynecological	**6-month**	**674.50**	**.24**	**.00**	**.39**	**.00**	**.025**
rs9397456 G v. A/GA	Gastrointestinal	12-month	483.00	.41	.00	.04	.00	.059
rs10484919	Vasomotor	12-month	288.00	2.41	1.00	3.46	2.00	.088
C v. CT	**Gastrointestinal**	**6-month**	**308.00**	**.19**	**.00**	**1.08**	**.00**	**.003**
rs12173570	**Gastrointestinal**	**6-month**	**600.50**	**.21**	**.00**	**.71**	**.00**	**.034**
C v. TC	**Weight concerns**	**Pre-AI**	**590.00**	**.45**	**.00**	**.95**	**.00**	**.016**
	Total	**Pre-AI**	**43.00**	**19.95**	**17.00**	**48.33**	**53.00**	**.043**
	Musculoskeletal	**Pre-AI**	**25.00**	**3.96**	**4.00**	**12.33**	**11.00**	**.016**
	Vasomotor	**Pre-AI**	**37.50**	**1.73**	**1.00**	**6.67**	**6.00**	**.026**
	Vasomotor	**6-month**	**43.00**	**2.61**	**2.00**	**6.33**	**7.00**	**.045**
	Vasomotor	12-month	46.50	2.51	2.00	5.00	4.00	.073
rs3778609	Gastrointestinal	Pre-AI	75.50	.42	.00	1.67	1.00	.089
C v. CT	**Gastrointestinal**	**6-month**	**64.00**	**.30**	**.00**	**1.33**	**1.00**	**.026**
	Gastrointestinal	**12-month**	**55.00**	**.27**	**.00**	**1.67**	**1.00**	**.022**
	Dyspareunia	12-month	46.50	1.51	1.00	.00	.00	.076
	Weight concerns	Pre-AI	76.00	.52	.00	2.00	1.00	.083
	Weight concerns	12-month	66.00	.29	.00	.67	1.00	.066
rs77275268 C v. CT	Gastrointestinal	6-month	424.50	.25	.00	.79	.00	.064
rs7761133 T v. TC	Musculoskeletal	6-month	512.00	5.25	4.00	7.00	7.00	.079
rs9383938	Cognitive	Pre-AI	343.50	2.28	2.00	1.15	.00	.035
G v. GT	Gastrointestinal	6-month	388.00	.24	.00	.85	.00	.037

Note*: Pre-AI = pre-therapy; Bold= p<.05*

Table 6 Adherence by *ESR1* SNVs 2-group Chi Square

SNV genotype	6 months		12 months	
	Odds Ratio (Confidence Interval)	p-value	Odds Ratio (Confidence Interval)	p-value
rs3778099 T vs CT	3.519 (1.043-11.874)	.069[FE]	**4.156 (1.223-14.125)**	**.036[FE]**
rs2234693 T/TC vs C	3.076 (.990-9.553)	.058[FE]	2.455 (.805-7.486)	.129[FE]
rs827421 T/TC vs C	2.667 (.910-7.812)	.082[FE]	2.522 (.896-7.102)	.075[FE]
rs6557171 C vs T/CT	1.490 (.539-4.119)	.441	2.438 (.914-6.503)	.071[FE]
rs9322331 C vs T/TC	2.120 (.636-7.060)	.214	3.273 (.875-12.246)	.069
rs9340799 A vs G/GA	2.216 (.664-7.392)	.188	2.665 (.808-8.785)	.099

Note: FE=Fisher's Exact Reference is Not adherent group= <80% adherence Bold= p<.05

Table 7 shows *PGR* SNVs that were beneath the screening cut point of p<.1. *PGR* SNVs were significantly associated with six of the eight symptom subscales and the total score for at least one timepoint. Several *PGR* SNVs were associated with adherence as shown in Table 8. One SNV, rs608995, remained significant (p<.05) at both timepoints. Women with the AA genotype had 4 times the odds of being in the adherent group than those with TT or AT genotypes (OR 4.000; 95% CI 1.360-11.763; p=.009 at 6 months; OR 2.708; 95% CI 1.013-7.243; p=.043 at 12 months).

Table 7 BCPT Symptoms by *PGR* SNVs 2-group Mann Whitney U (p<.1)

SNV/ genotype Group 1 v. Group 2	BCPT Subscale	Time	U	Group 1		Group 2		p-value
				Mean	Median	Mean	Median	
rs1042838 G vs T/GT	**Musculoskeletal**	**Pre-AI**	**557.00**	**4.68**	**4.00**	**2.95**	**2.00**	**.022**
	Gastrointestinal	Pre-AI	640.50	.37	.00	.78	.00	.049
	Gastrointestinal	12-month	453.50	.24	.00	.61	.00	.077
rs1042839 C vs T/TC	Musculoskeletal	Pre-AI	496.00	4.61	4.00	3.16	3.00	.089
	Gastrointestinal	**Pre-AI**	**454.50**	**.36**	**.00**	**.95**	**1.00**	**.008**
	Gastrointestinal	**12-month**	**342.50**	**.25**	**.00**	**.73**	**.00**	**.031**
rs1893505 C vs T/CT	Weight concerns	Pre-AI	898.00	.29	.00	.71	.00	.063
rs10895068 G vs AG	Gynecologic	6-month	358.00	.31	.00	.50	.00	.080
rs11224561 C vs TC	Musculoskeletal	6-month	543.00	5.30	5.00	6.48	7.00	.082
	Vasomotor	6-month	544.00	2.87	2.00	2.00	1.00	.080
	Bladder	Pre-AI	607.50	.68	.00	1.18	1.00	.074
	Bladder	6-month	562.00	.90	.00	1.24	1.00	.079
	Bladder	12-month	404.50	.89	.00	1.56	1.00	.053
rs471767 A vs G/AG	**Vasomotor**	**12-month**	**593.00**	**3.02**	**2.50**	**2.30**	**2.00**	**.033**
rs1942836 T vs C/TC	**Gynecologic**	**Pre-AI**	**819.00**	**.23**	**.00**	**.57**	**.00**	**.022**
rs474320 T vs A/AT	**Musculoskeletal**	**Pre-AI**	**599.00**	**4.68**	**4.00**	**3.04**	**2.00**	**.038**
	Gastrointestinal	**Pre-AI**	**653.50**	**.36**	**.00**	**.78**	**.00**	**.041**
	Gastrointestinal	**12-month**	**434.50**	**.23**	**.00**	**.65**	**.00**	**.045**
rs4754732 T vs C/TC	Cognitive	Pre-AI	895.50	1.67	1.00	2.42	2.00	.097
rs484389 T vs C/TC	Gastrointestinal	Pre-AI	892.50	.24	.00	.72	.00	.064
rs568157 A vs G/GA	**Total**	**Pre-AI**	**635.00**	**15.34**	**14.00**	**22.91**	**19.00**	**.029**
	Total	6-month	640.50	19.80	18.00	24.68	21.00	.069
	Cognitive	**Pre-AI**	**564.00**	**1.08**	**.00**	**2.48**	**2.00**	**.005**
	Musculoskeletal	**6-month**	**577.50**	**4.44**	**3.00**	**6.06**	**6.00**	**.018**
	Vasomotor	Pre-AI	688.00	1.04	1.00	2.21	2.00	.069
	Gastrointestinal	Pre-AI	716.00	.16	.00	.56	.00	.051
rs590688 C vs G/CG	**Gastrointestinal**	**12-month**	**502.00**	**.09**	**.00**	**.44**	**.00**	**.037**
	Weight concerns	**12-month**	**502.50**	**.09**	**.00**	**.40**	**.00**	**.038**
rs608995 A vs T/AT	Gastrointestinal	6-month	990.00	.33	.00	.45	.00	.085

Note: Pre-AI = pre-therapy; Bold indicates p<.05

Table 8 Adherence by *PGR* SNVs 2-group Chi Square (p<.1)

SNV genotype	6 months		12 months	
	Odds Ratio (Confidence Interval)	p-value	Odds Ratio (Confidence Interval)	p-value
rs1042838 G vs T/GT	**3.729 (1.275-10.904)**	**.019 FE**	2.163 (.757-6.179)	.144
rs1042839 C vs T/TC	3.325 (1.054-10.492)	.050 FE	2.250 (.704-7.196)	.199 **FE**
rs10895068 G vs AG	.831 (.748-.923)	.064 FE	**.800 (.708-.903)**	**.034 FE**
rs11224561 C vs TC	**.718 (.621-.831)**	**.010 FE**	1.176 (.394-3.517)	.771
rs1942836 T vs C/TC	.269 (.072-1.004)	.059FE	**.293 (.090-.957)**	**.035**
rs474320 T vs A/AT	**3.857 (1.320-11.269)**	**.017 FE**	2.245 (.787-6.404)	.125
rs484389 T vs C/TC	**3.833 (1.301-11.291)**	**.011**	2.329 (.888-6.107)	.082
rs608995 A vs T/AT	**4.000 (1.360-11.763)**	**.009**	**2.708 (1.013-7.243)**	**.043**

Note: *FE=Fisher's Exact*
Bold indicates p<.05

These findings suggest potentially, women who are married have some type of support for better adherence and women in the chemotherapy group initially experience more symptoms that wane over time. Additionally, *ESR1* polymorphisms are more associated with symptoms than adherence, and *PGR* polymorphisms are more strongly associated with adherence than symptoms. These findings suggest potential underlying biological mechanisms as a source of symptoms and adherence. However, these exploratory analyses did not correct for multiple testing and must be interpreted with care.

1.3.3 Study 3

We examined associations among symptom scores from the Breast Cancer Prevention Trial (BCPT) checklist and baseline (pre-anastrozole) medication regimens in the same sample of

women with early-stage breast cancer used for Aim 3 (n=97). There was no correlation between total BCPT score and the number of medications. However, when looking at the type of baseline (pre-anastrozole) medication categories, women reported more symptoms when they took thyroid medications (mean 27.46 ±16.88 vs none 19.35 ±13.87; p=0.031), anti-depressants (mean 32.86 ±18.82 vs none 17.88 ±11.89; p=0.002), and gastric reflux preparations/anti-peptic agents/prostaglandins (mean 28.09 ±16.92 vs none 18.61±13.31; p= 0.017). Additionally, women who took calcium/calcium with vitamin D (mean 18.49 ±11.80; p= 0.068) reported fewer symptoms than those without calcium supplementation (mean 24.47 ±17.84).

These preliminary results suggest that baseline (pre-anastrozole) medication categories and/or the condition for which they are taken have some role in symptoms experienced. Baseline (pre-anastrozole) medication regimens and/or the condition for which they are prescribed/taken may produce an additive effect on symptoms as an inducer of AI ADME or act independently of the AI to influence symptoms.

1.4 Innovation

Group-based trajectory modeling (GBTM) categorizes patients by membership in groups based on the temporal pattern, or trajectory, of a variable (Nagin & Odgers, 2010a, 2010b). GBTM provides a holistic view of symptoms and adherence by taking into account the dynamic change over time. This statistical method has been used to examine symptoms (Rottmann et al., 2016; Wang et al., 2016), primarily for a single symptom type. It has also been used to examine medication adherence trajectories (Franklin et al., 2013). Three studies utilized GBTM to examine endocrine therapy adherence drug refill records (Lambert-Cote et al., 2020; Winn & Dusetzina,

2016; Winn et al., 2019). To date, no studies have used GBTM with MEMS® data. The dissertation study will provide vital insight into symptoms over time, as well as the daily AI adherence (Aim 1).

Using identifying patterns of symptoms and adherence and their potential relationship in a dual trajectory of adherence and symptoms we will, for the first time, assess the potential temporal influence of these variables on each other (Aim 2). For example, instances of decreased adherence may be related to increased symptoms. If the trajectories are associated temporally, interventions can be developed to improve both.

Perceived economic hardship is often thought to impact adherence, and examination of this variable is a high priority (Carrera et al., 2018). Economic hardship may also increase stress and affect other symptoms (Altice et al., 2017). This variable differs from income and cost analyses in that the patient's perception transcends typical economic measurement. It is being treated as a self-reported symptom in these analyses. In addition, we will use income and employment as phenotypic covariates.

Finally, few studies have evaluated genomic influence on the ADME of anastrozole (Abubakar et al., 2014; Artigalas et al., 2015; Gervasini et al., 2017). Results in other drugs have shown that the ADME pathway is a useful clinical tool with which to tailor medication therapies. Identifying genetic variation in anastrozole ADME pathways of symptom development will lay the groundwork to shift in the paradigm for AI therapy from symptom-reactive to a symptom-proactive, adherence-proactive approach.

This study explores genotypes and phenotypes to describe and examine complex relationships among AI adherence, ADME factors, symptoms. This study will provide clinicians with insight into patterns of temporal changes for AI adherence and symptoms, as well as

phenotypic and genotypic (ADME) risk factors, and therefore provide critical information to develop future interventions that improve adherence and outcomes in women with BC.

1.5 Approach

1.5.1 Study Design

We will conduct an analysis of existing prospectively collected longitudinal data from three parent studies (from this point referred to as 'parent study': Anastrozole Use in Menopausal Women R01CA107408, PI: Bender; Predictors of Adherence to Hormonal Therapy in Breast Cancer Oncology Nursing Foundation, PI: Bender; and Genomics of Cognitive Function in Breast Cancer Oncology Nursing Foundation, PIs: Conley and Bender). In addition, we will generate new germline genomic data from existing banked samples. For the dissertation study, women who have adherence, symptom, and/or genomic data from the parent study will be included, and sample sizes will be based upon dissertation study aims.

1.5.2 Hypothesis

This dissertation study will describe and examine complex relationships among AI adherence, symptoms, and genotypic and phenotypic factors (Figure 3).

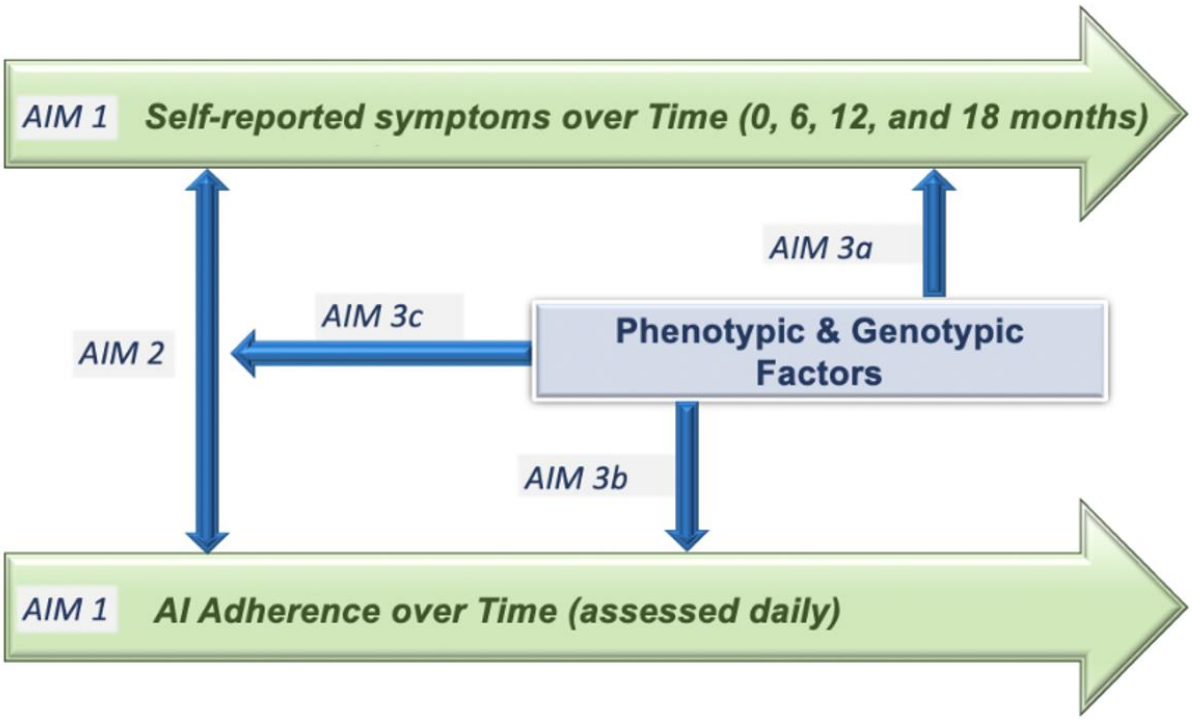


Figure 3 Study Aims

We hypothesize that: women taking anastrozole can be phenotypically classified into distinct subgroups by symptom experience and adherence trajectories over time (Aim 1), and there is a relationship between symptom and adherence subgroup classifications (Aim 2).

Additionally, we will explore whether the subgroup classifications are modified by covariates, e.g., ADME genotypes and phenotypes (Aims 3a, 3b, 3c).

1.5.3 Sample

The dissertation study is a secondary analysis, which will use prospectively collected longitudinal data from the parent study. Participants were followed for a period of at least 18 months. Enrollment criteria for inclusion to the parent study were age 18-75 years; diagnosed with stage I-IIIa breast cancer based on the Tumor, Node, Metastasis Classification System (*AJCC*

(American Joint Committee on Cancer) Cancer Staging Manual., 2018) (also confirmed by the participant's medical oncologist or medical record); post primary surgery with/without chemotherapy; eligible to receive AI therapy; able to speak and read English (Lezak, 1995); and completed at least 8 years of education (Lezak, 1995). Participants were excluded if they had a psychiatric hospitalization within the last 2 years (Valentine et al., 1998); a prior neurologic condition diagnosis such as HIV-related dementia, Parkinson's disease, dementia syndrome, stroke, multiple sclerosis, or chronic fatigue syndrome (Lezak, 1995); clinical evidence of distant metastases including the CNS (Gordon, 1978); or a prior diagnosis of invasive cancer other than non-melanoma skin cancer (Silberfarb, 1983).

Women who have adherence and symptom data will be included to address Aims 1 and 2 (N=360 for symptoms and N=291 for adherence and dual trajectories). Women who additionally have genomic data will be included in the portion of Aim 3 pertaining to the exploratory genomic analyses (N=122).

1.5.3.1 Setting

Postmenopausal women with BC were recruited from the Comprehensive Breast Program (CBP) of the UPMC Hillman Cancer Center (HCC), an NCI-designated Comprehensive Cancer Program. The CBP included seven clinical sites. Data were collected at these sites or in participants' homes per their choice.

1.5.4 Sample Size

The sample size was originally estimated at 338. Please note that when determining power for overview, we used sample sizes of N=338 for Aims 1 & 2 and N=97 for exploratory Aim 3.

Based on our criteria of anastrozole being the participant's initial AI and on the results of our preliminary work (see section 3.0), we were able to increase the sample to N=360 for symptom trajectories and N=291 for adherence and dual trajectories (Aims 1, 2) and N=122 (exploratory Aim 3 for genomics).

1.5.4.1 Aim 1 Symptoms

Given the fixed sample of 338 of which 32% are in group X=0 not married and 68% are in group X=1 married, and given this analyses results in 2 distinct trajectory classes we would have at least 80% power at a two-tailed significance (alpha) of less than 0.05 to detect a change of 0.100 to 0.239 for categorical nongenetic baseline predictors and covariates (clinical predictors, sociodemographics) on symptoms with an odds ratio (OR) as small as 2.829 when there is an R squared of 0.20 among symptoms and covariates (Hsieh et al., 1998).

For continuous nongenetic baseline predictors and covariates (pre-anastrozole medication regimens, comorbid conditions) and N=338, we have at least 80% power at two-tailed significance of less than 0.05 to detect a change in the mean from .100 to .164 when increased by one standard deviation resulting in an odds ratio as small as 1.765. An adjustment was made since the multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R squared of 0.200 (Hsieh et al., 1998). We will use a logistic regression model (multinomial if >2 groups) to compare the odds of classification within each trajectory for predictors and covariates.

1.5.4.2 Aim 1 Adherence

Given the fixed sample, if adherence produces 2 distinct trajectory classes with a 50% chance of adherence, we would have at least 80% power at a two-tailed significance of less than

0.05 to detect a change in the baseline value from 0.500 to 0.678 for our categorical nongenetic baseline predictors and covariates (clinical predictors, sociodemographics) on adherence with an OR as small as 2.104 when there is 20% correlation among covariates (Hsieh et al., 1998)

For continuous nongenetic baseline predictors and covariates (concurrent medication regimens, comorbid conditions) and N=338, we have at least 80% power at two-tailed significance of less than 0.05 to detect a change in the mean from .500 to .584 when increased by one standard deviation resulting in an odds ratio as small as 1.406. An adjustment was made since the multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R squared of 0.200 (Hsieh et al., 1998). We will use a logistic regression model (multinomial if >2 groups) to compare the odds of classification within each trajectory for predictors and covariates.

1.5.4.3 Aim 2 Dual Trajectory

We will compare trajectory classes from adherence and symptoms in a contingency table using chi-square. For a combined sample of 338 to examine 2 adherence and 2 symptom classes, with 1 degree of freedom *(df)*, we have 80% power at 2-tailed alpha less than 0.05 to detect an effect size W=0.1879 and chi-square of 11.9353 (Hsieh et al., 1998). We will use a logistic regression model (multinomial if >2 groups) to compare the odds of classification within each trajectory for predictors and covariates.

1.5.4.4 Aim 3 Predictors

This aim is exploratory, and no sample size calculation was completed. We will use a multinomial logistic regression model to compare to determine the odds of classification within each trajectory for genotype as a predictor of group membership.

1.5.5 Measurement of Variables

The following section describes measures used for symptom and adherence phenotypes and genotypes.

1.5.5.1 Symptom Phenotypes

We will examine self-reported symptoms (Table 2), collected via a pen and paper survey at baseline (pre-anastrozole), and at 6-, 12-, and 18-months post-initiation of anastrozole. Except when otherwise specified, data from each measure will be examined in bivariate analyses with adherence to identify relationships. We may examine relationships with a measure's total score, subscale, or single question.

The Breast Cancer Prevention Trial (BCPT) checklist (Ganz et al., 1995; Ganz et al., 2000; Stanton, 2005; Terhorst et al., 2011) is a self-report measure of the degree to which women have been bothered by 42 hormone therapy- and menopausal-related symptoms in the past 4 weeks (Ganz, 2000; Stanton, 2005). The measure is comprised of eight subscales: vasomotor, gastrointestinal, bladder, gynecological, dyspareunia, musculoskeletal, cognitive, and weight problems. Subjects rate symptoms on a 5-point Likert scale (0 = not at all to 4 = extremely). Subscale scores are the average score for items in each subscale, the total score is the average score across all items. Cronbach's alphas for subscale scores range from .43 to .83 for women with breast cancer receiving hormonal therapy.

The Brief Pain Inventory (BPI) (Atkinson et al., 2011; Daut et al., 1983) assesses pain level and pain interference with activities using an 11-item survey. Four questions ask participants to rate their pain from 0 (no pain) to 10 (pain as bad as you could imagine) at its worst and least in the last 24 hours, on average, and now. Seven questions focus on pain interference with activity,

mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, on a scale of 0 (does not interfere) to 10 (interferes completely).

The Profile of Mood States (POMS) (Norcross et al., 1984) measures anxiety and fatigue. The Profile of Mood States (POMS) Tension-Anxiety subscale is a 9-item, self-report subscale in which adjectives are rated on a 5-point Likert scale (McNair, 1992). The score is the sum of responses for items. Internal consistency was .92 and test-retest reliability was .70 in 1000 psychiatric outpatients (McNair, 1992). The POMS is sensitive to changes in anxiety levels in patients with cancer (Cassileth et al., 1992).

Fatigue is measured using the Fatigue/Inertia Subscale of the POMS. It is a 7-item self-report subscale in which adjectives are rated on a 5-point Likert scale (McNair, 1992). The score is the sum of responses for items. Internal consistency of the Fatigue-Inertia subscale was .94 and test-retest reliability was .66 in 1000 psychiatric outpatients (McNair, 1992).

The Beck Depression Inventory-II (BDI) (Beck et al., 1996; Wang & Gorenstein, 2013) is a self-report of depressive symptoms and attitudes on a 4-point Likert scale (Beck et al., 1996). The score is the sum of responses for items. The Cronbach alpha coefficient for 500 outpatients with mental disorders was .92 and .93 for 120 college students. The BDI correlates strongly with the major depression episode portion of the Structured Clinical Interview for DSM-IV Axis I Disorders (.83) (Sprinkle et al., 2002; Stukenberg et al., 1990) and the Revised Hamilton Rating Scale for Depression (.71) (Beck et al., 1996; Spreen & Strauss, 1998). The total score will be used for this study.

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) assesses sleep quality over the previous month. Overall reliability of the component is good at .83 (Cronbach's alpha) and the

instrument is reliable (kappa = 0.75, $p < 0.001$). Women with poor sleep quality had nearly twice the odds of discontinuing their AI (Kidwell et al., 2014).

To complement the PSQI, we will also use the Epworth Sleepiness Scale (Johns, 1991), This is a reliable measure of daytime sleepiness with Cronbach's alphas are between 0.73-0.86 (Kendzerska et al., 2014).

The Psychological Sense of Economic Hardship (Barrera et al., 2001) assesses perceived economic hardship in 4 different domains: 1) financial strain (r = .73-.75); 2) inability to make ends meet (r = .70 - .76); 3) not enough money for necessities (α = .80-.85); and 4) economic cutbacks and adjustments (α = .70 - .73). The financial strain, inability to make ends meet and not enough money for necessities are rated on a 5-point Likert-type scale and mean subscale scores are created. Economic adjustments and cutbacks are assessed with nine items such as added another job, received government assistance, and sold possessions because money was needed. Participants indicate whether these events have occurred in the past month. This subscale score is the total number of events that occurred (0–9). Economic hardship is being treated as a self-reported symptom in these analyses. It is often thought to impact adherence in cancer survivors from 4% to 73%, but it may also increase stress and affect other symptoms (Altice et al., 2017; Gordon et al., 2017). This variable differs from income and cost analyses in that the patient's viewpoint transcends typical economic measurement.

1.5.5.2 Phenotypes for Adherence to Anastrozole

AI adherence was assessed continuously for 18 months with the MEMS® Medication Event Monitoring System (MEMS®) (AARDEX Group SA, 2022). MEMS® records a date/time stamp for each cap opening with a battery life of up to 3 years and capability of recording 3800 dose events (AARDEX Group SA, 2022), more than sufficient for 18 months of daily use. Data

were downloaded by scanning the cap using a communicator component every 6 months. Software enabled personnel to view data and verbally confirm cap function and use by the participant. (These self-reported data at the time of download are also used in this project). Any reasons for not using the cap were tracked and dates and reasons were recorded. These periods of time are not included in calculations. Adherence is summarized as a proportion/percentage: doses taken/doses prescribed x 100. The range is 0-100%, with 100% representing perfect adherence. We will also consider calculating adherence with dose timing, but with anastrozole's long half-life, this calculation is not therapeutically informative (Drugs.com, 2000-2018). Chronic disease and oncology researchers use a cut point of ≥80% to consider adherence (Murphy et al., 2012; Thier et al., 2008). However, it should be noted that this cut point is used by convention, rather than being used based on drug half-life (Cramer et al., 2008).

1.5.5.3 AI ADME Factors of Genotypes and Baseline (Pre-anastrozole) Medication Regimens

Candidate genes and/or pre-anastrozole medication regimens used by participants will be the ADME factors. Potential candidate genes for this study were chosen based on current literature and their known or potential role in AI ADME, for symptom development for AIs, for the role as the drug target, and for their role as hormonal receptors (see Table 9)(Edavana et al., 2013; Gervasini et al., 2017; Daniel L Hertz et al., 2017; Kamdem et al., 2010; Wang et al., 2010). Most candidate genes are part of the cytochrome P450 drug metabolism system, drug transporters, and metabolite regulators, and Figure 4 shows their connections derived from literature (Szklarczyk et al., 2019). However, if it becomes apparent that other pathways may be involved, we may add genes. Baseline (pre-anastrozole) medication regimens were assessed via participant self-report and confirmed by medical record data.

Table 9 Potential candidate AI ADME, target, and receptor genes

Genes	Name	AI ADME / Target / Receptor Function
CYP3A4/5/7	Cytochrome P450 Family 3 Subfamily A Member 4, 5 and 7	Anastrozole hydroxylation
UGT1A4	UDP Glucuronosyltransferase Family 1 Member A4	Anastrozole glucuronidation
ABCB1	ATP Binding Cassette Subfamily B Member 1	Efflux pump, transporter
ABCC2	ATP Binding Cassette Subfamily C Member 2	
CYP2C8	Cytochrome P450 Family 2 Subfamily C Member 8	Anastrozole hydroxylation
CYP2D6	Cytochrome P450 Family 2 Subfamily D Member 6	
CYP2B6	Cytochrome P450 Family 2 Subfamily B Member 6	
UGT2B7	UDP Glucuronosyltransferase Family 2 Member B7	Anastrozole glucuronidation
CYP19A1	Aromatase	Drug target, converts androgens to estrogens
ESR1/2	Estrogen receptor 1 and 2	Hormone receptors
PGR	Progesterone receptor	

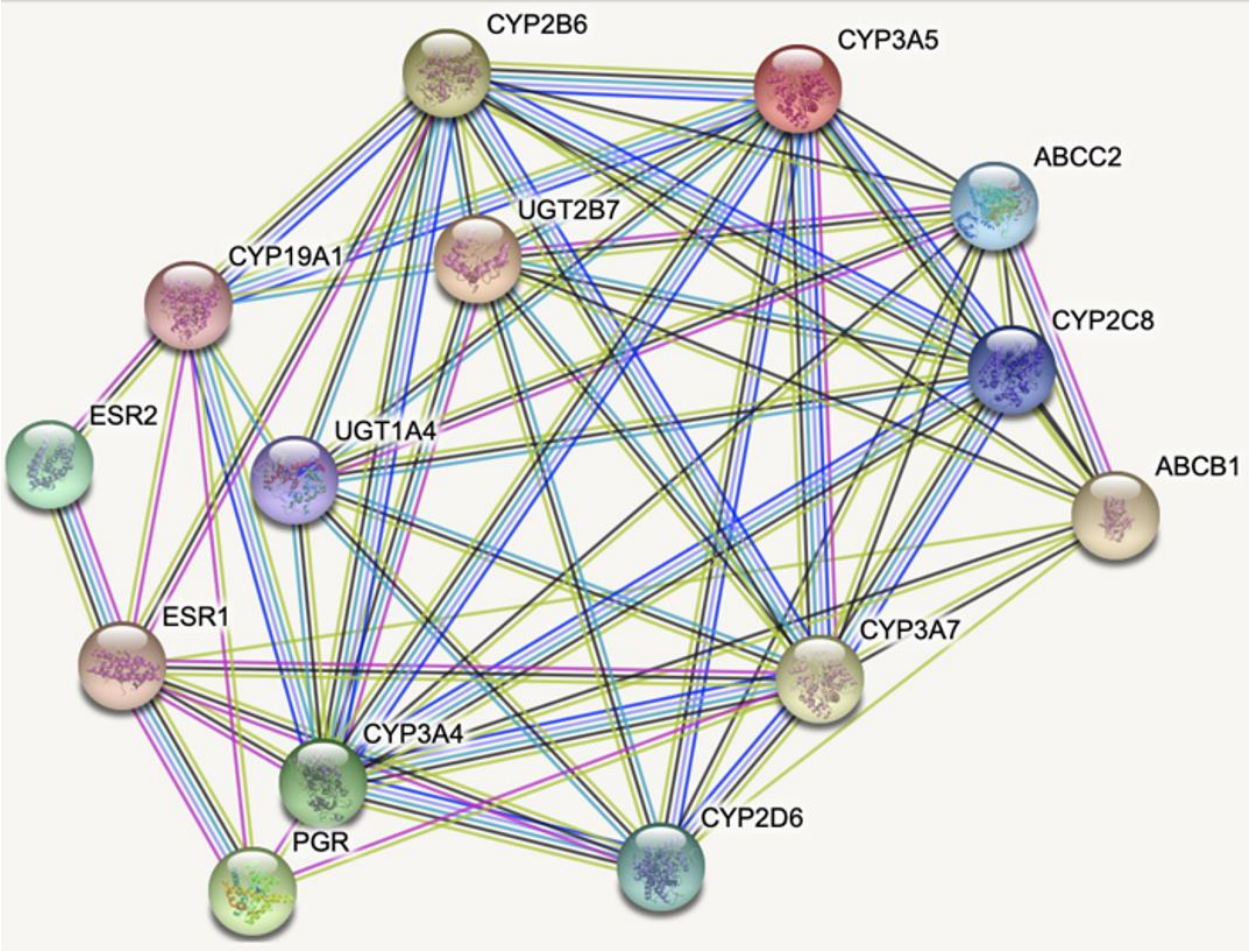


Figure 4 Connections Among Candidate Genes

Note: free, publicly-accessible resource STRING-db.org (Szklarczyk et al., 2019)

Information collected consisted of drug names, condition categories based on drugs listed, and the total number of medications.

1.5.6 Genomic Data Collection and Processing.

Genomic samples were collected via (1) blood or (2) saliva. The sample was logged in and centrifuged and white cells were removed. DNA was extracted from white cells used a simple salting out procedure (Miller et al., 1988). Saliva collection used the Oragene™ DNA self-

collection kit from DNA Genotek Corporation. Product protocol, including the use of the reagents for extraction in the Oragene™ kit, was followed. DNA was stored in 1X TE buffer at 4°C. Within 48 hours of collection, samples were processed and DNA was extracted, aliquoted, diluted, and placed in a -80°C freezer for banking. Either the iPLEX® Agena Bioscience MassARRAY® platform for genotyping (Ellis & Ong, 2016) or PCR and gel electrophoresis will be used.

1.5.6.1 Phenotypic Covariates

Covariates were collected at baseline (pre-anastrozole) and at 6-, 12-, and 18-months post-initiation of the drug unless otherwise noted. Sociodemographic data were collected by a pen and paper survey completed by the participant to assess pertinent social and demographic characteristics (age, marital status, education, income, employment). Clinical data that may influence adherence, including tumor type and cancer staging (Aiello Bowles et al., 2012), were collected at baseline by study nurses using pathology and physician reports in the electronic health record. Comorbid conditions data were provided by the participant and confirmed by medical record data. Comorbid conditions may influence symptoms or adherence. There is no scoring, but condition categories derived from the medication list and the total number of medications taken will be used.

1.5.7 Scientific Rigor and Reproducibility

Laboratory data have been collected and stored by research nurses and experienced laboratory personnel. When processing genomic data for candidate genes, established quality control procedures will be followed and duplicate controls on each plate for internal and plate-to-plate consistency will be used. Specifically, quality controls will include a well with an additional

DNA sample that previously performed well in iPLEX®; a well without DNA (a no template control) to assess for cross-contamination; and a well without Taq polymerase and no amplification (to assess for noise in the data on the plate) (Ellis & Ong, 2016). We will compare allele frequencies to frequencies in databases such as the 1000 Genomes and HapMap projects and will assess Hardy-Weinberg Equilibrium (HWE) consistency. SNVs not meeting quality control standards and SNVs with a call rate of less than 90% will not be used. Parent study phenotypic data have been collected, entered, cleaned, and quality checked following standard operating procedures by experienced research personnel. Data are regularly backed up at the Pitt Network Operations Center (NOC) and on School of Nursing servers (all servers are behind the Pitt firewall). MEMS® caps were checked for accuracy prior to assigning them to the participants and every 6 months throughout the study. Suspected defective caps were replaced immediately.

1.5.8 Data Analysis

We will conduct a detailed descriptive and exploratory analysis of the variables and examine the data for accuracy by proofreading the data, examining descriptive statistics and graphs, checking ranges, and contingency checking.

1.5.8.1 Outlier Assessment

Univariately for each variable, descriptive statistics will be used to initially screen for out-of-range values. For categorical data, a frequency table will be examined for the distribution among cells. Continuous variable frequencies with graphic representation of the data will be assessed, for example, boxplot and histogram. Next, we will create Z-scores using descriptive statistics and saving standardized values as Z-scores. Next the Z-score distribution will be assessed for outliers

>3.29 and <-3.29. If a data point is an outlier, a check will be done to ensure the outlier is not related to other variables (multivariate outlier assessment, Mahalanobis distance). Next, a determination will be made about modifying the value. Analyses will be run with and without the altered variable. The outliers will be evaluated for independence, normality and multivariate normality, linearity, and homoskedasticity.

1.5.8.2 Data Transformations

Every attempt will be made to avoid transforming data values into nonclinical values. In the case of skewed distributions, it may be necessary to meaningfully categorize continuous variables. For example, adherence data may be categorized into adherent/not adherent for some analyses. When a categorical variable does not have enough cases in a category, categories will need to be meaningfully collapsed prior to analyzing. For example, rare homozygous genotypes will need to be combined with heterozygous genotypes in order to provide enough cases per cell for multivariate analyses.

1.5.8.3 Missing Data

We will describe the number of missing observations/cases univariately and multivariately. We will examine attrition and missingness for patterns, such as missing at random versus not at random. If missing values are greater than 20%, the variable will not be included in the analyses. Then we will determine how to treat missing values: 1) analyze only complete cases 2) analyze available information or 3) impute missing values. This will depend on the variables and their role in an analysis. For example, if the variable's role is that of an independent variable, we may remove the case; conversely, if it is a dependent variable, we may choose to estimate parameters using the

full information maximum likelihood (FIML) method, an unbiased estimate that uses observed complete data and implied probable values.

1.5.8.4 Assumptions

Chi-square test of independence assumes the variables have nominal scaling, independence of observations, the sample should be random and large/varied enough to fill every cell. The expected cell count is not large enough (often the cutoff is 5), then Fisher's Exact test will be used. Parametric descriptive tests (e.g., means, standard deviations) require normally distributed data with equal population variances, independent observations, and random sample. Nonparametric robust descriptive testing using medians, Mann Whitney U, and Kruskal-Wallis test will be used when assumptions of normal distributions are not met.

1.5.8.5 Screening Variables for Correlations

After univariate analyses are complete, variables will be compared with each other to identify highly correlated variables. Categorical (nominal/ordinal) variables can be compared in contingency tables with chi-square test for independence. Interval and ratio scaled variables can be assessed visually by using a scatterplot, examining direction and magnitude of association. The correlation coefficient can provide the statistic for the magnitude and direction of an association (Pearson's product-moment coefficient for parametric correlation and Spearman's Rho for nonparametric correlation). Assumptions for correlations are independent observations, normal bivariate distribution, random variables that are interval or ratio, and a linear pattern. A linear regression can also be used to determine a relationship between 2 variables (or more for multiple linear regression). Assumptions are a linear relationship, multivariate normality, no multicollinearity (variables highly correlated with each other; check correlation matrix and

variance inflation factor<10), independence of error terms, and homoscedasticity (residuals are equal across the regression line). Leverage is assessed for influential data points. Corrections (remedial strategies) may be made to have the data fit and meet assumptions. Similar to linear regression, logistic regression may also be used to assess relationships among 2 or more variables, prior to determination of the final model. By assessing variables first and eliminating highly correlated variables as well as variables that appear to have no effect, one can create the most parsimonious model.

1.5.9 Preliminary Symptom Data Reduction

The following is summarized in section 3 with corresponding tables or figures in Appendix A.

A comprehensive trajectory analysis of available symptom data would have resulted in 8-25 separate trajectory analyses for Aim 1. Therefore, to reduce the symptom data for the proposed trajectory analyses in Aims 1 and 2, we examined symptom data using a multi-layered process.

The first step in examining the symptom data was to correlate each subtotal or total (if the measure did not have subscales) with all other symptom scores. The following measures have subscales: BCPT (8); BPI (2); POMS (2); PSQI (7); and Economic Hardship (4). Results are shown in detail in Appendix A. We found that the Beck Depression Inventory, the POMS fatigue and anxiety subscales and the BCPT cognitive subscale were the most strongly correlated symptoms across all 4 timepoints (pre-anastrozole, 6-, 12-, and 18-months).

Next, we conducted factor analyses to determine if these correlations would load together on one dimension. The forced five-factor model that explained a large proportion of the variance and included the following 5 dimensions with the BCPT cognitive subscale, Beck Depression

Inventory, POMS anxiety subscale, and POMS fatigue subscale (called neuropsychological symptom burden or NSB) loading most strongly.

Of note, several factor dimensions, particularly NSB, had measures that consistently loaded with each other, while others had highest dimension loadings when alone. Pain (BPI subscales and BCPT musculoskeletal subscale) consistently loaded on one dimension and improved the variance explained when *removed*, which was the reason we removed it from this analysis. These dimensions each load on a particular concept, thus one dimension should be chosen for a trajectory analysis (rather than all combined into one analysis).

Sample and data variation are important considerations in both factor analysis and trajectory analysis. For factor analysis, the sample size is key to determining a valid dimensional assessment. A sample size of 200 is "fair" (Comrey & Lee, 1992; MacCallum et al., 2001; Pearson & Mundform, 2010). Further, sample size is key to conducting a trajectory analysis (Loughran & Nagin, 2006). The number of trajectories possible depends upon the sample size and distribution of subjects across trajectories as well as data variability. For example, it would not be informative to have all participants fall into one trajectory. Therefore, sample size was taken into consideration when choosing symptoms to be used. Although sleep and economic hardship are key symptoms, the sample taking anastrozole was too small for an informative trajectory analysis.

Finally, we searched the literature to inform our choice of symptoms for Aims 1 and 2. However, literature in symptoms and adherence in women with breast cancer is not particularly informative when choosing a dimension. Most studies have focused on one symptom or set of similar symptoms. Our postulation is that no one symptom is as important to adherence as the overall symptom burden patients experience, and that there may be underlying, pre-existing symptoms that affect adherence. Preliminary correlations we conducted on symptoms, specifically

economic hardship correlations with other symptoms, led us to consider this possibility. The literature also supports using sets of co-occurring symptoms such as symptom clusters (Li et al., 2020; Miaskowski, 2016; Miaskowski et al., 2017).

Based on preliminary analyses, sample considerations, and the literature review, we will use the neuropsychological symptom burden dimension, which includes BCPT cognitive subscale, Beck Depression Inventory, POMS anxiety subscale, and POMS fatigue subscale for the symptom trajectory. This dimension will serve as an exemplar for the symptom experience. Other researchers have used a similar group of symptoms (Park et al., 2020). Thus, in terms of symptom trajectories, we will use a composite score for neuropsychological symptom burden (NSB). Details on the results are in section 3.0.

1.5.10 Data Analysis for Study Aims

Data analysis will be conducted using IBM® SPSS® Statistics for Macintosh, Version 25.0 (IBM Corp., Armonk, NY) for descriptive statistics and regressions, and SAS for Windows (version 9.4, SAS Institute, Inc., Cary NC) for group-based trajectory modeling (GBTM). The level of statistical significance will be set at .05 for non-directional (two-sided) hypothesis testing and confidence intervals will be set at 95% for interval estimation. There will be no corrections for multiple testing.

1.5.10.1 Data Analysis Aim 1.

We will separately utilize group-based trajectory modeling (GBTM) for (1) anastrozole adherence and (2) symptoms. GBTM will categorize groups of participants by anastrozole adherence or symptoms by patient factors (Li et al., 2014; Nagin & Odgers, 2010a). GBTM is a

statistical method used to examine longitudinal data prospectively without losing detail. Most longitudinal analyses average data over time or utilize a choice of intervals. GBTM identifies distinct trajectories by the variable trajectory, graphing the course of the variable of interest over time (Nagin & Odgers, 2010a, 2010b). For example, one group may adhere well at the beginning and drop sharply after a month; another group may slowly decline over time. This method offers some flexibility with non-normal distributed data and can be modeled as a binary variable when data are not normally distributed, as is the case for adherence. GBTM examines time-dependent and time-variant covariates and how they relate to the trajectory.

To accommodate and evaluate temporal pattern changes in adherence and symptoms, we will utilize GBTM for AI adherence or symptoms separately and identify distinct groups of participants by AI adherence and symptoms and patient factors (Nagin & Odgers, 2010a). GBTM is a way to examine longitudinal data prospectively without losing detail. GBTM categorizes participants by the shape of the variable's trajectory, graphing the course of the variable of interest over time, as a function of time, into distinct latent classes.(Li et al., 2014; Nagin & Odgers, 2010a, 2010b) This method examines the dynamic nature of the dependent variable (Aim 1 adherence and self-reported symptoms) (Nagin, 2014) and has been used to evaluate changes over time for adherence in other populations (Franklin et al., 2013) and symptoms (Merriman et al., 2010; Merriman et al., 2017) in cancer populations. An adherence study looking at once daily statins, using pharmacy refill data, GBTM was employed and found 6 distinct classes: one (23.4%) stayed adherent (set at ≥80% proportion of days covered); 11.4% moved from not adherent to adherent; 11.3% decreased adherence slowly over time; 15% were "occasionally" adherent; 19.3% decreased adherence sharply after starting; and 23.4% rarely filled their prescription (Franklin et al., 2013). Few AI studies employing use of adherence trajectory analysis (Lambert-Cote et al.,

2020; Winn & Dusetzina, 2016; Winn et al., 2019). One used claims data for endocrine therapy to examine trajectories and found 5 distinct groups (Lambert-Cote et al., 2020). The sample was about twice the size of this study (N=674) and the groups were characterized as "quick decline and stop" (5.2%), "moderate decline and stop" (6.4%), "slow decline" (17.2%), "high adherence" (30.0%), and "maintenance of very high adherence" (41.2%) (Lambert-Cote et al., 2020). With our sample we hypothesize that we will be able to categorize at least 2 distinct latent classes for our analysis. After we establish at least 2 trajectory classes, we will conduct binary logistic regression (multinomial regression if more than 2 classes) using non-genetic predictors, such as age, tumor stage, marital status, and medication regimen complexity. Three distinct latent classes were identified for cognitive symptoms in this sample of women with breast cancer, described as "more frequent" (8.8%); "persistent" (16.3%); and "almost never" (74.9%) (Merriman et al., 2017). We hypothesize that Aim 1 will find at least two distinct latent classes, and we will compare classes and non-genetic predictors as we did with the adherence model. Finally, we will use dual group-based trajectory modeling statistical methods to estimate joint and conditional probabilities of the anastrozole adherence and symptom trajectories (Nagin & Tremblay, 2001). Bayesian Information Criteria (BIC) and estimated distinct latent class membership probabilities will be used to choose the best fitting trajectory model for each aim. A limitation for this model is that an event could alter the trajectory, and the assumption is that there is no homogeneity and conditional independence (Nagin, 2014). To test overall model fit for logistic regression, we will assess the Hosmer-Lemeshow goodness of fit test, model deviance, and pseudo *R*-square. We will check for outliers and influential points with Pearson and deviance residuals and DFBETA, respectively. We will assess for covariate patterns by assessing leverage, and we will check for multicollinearity with the variance inflation factor. Residual and partial residual plots and addition of interaction

terms will round out the post model assessment for logistic regression. For linear regression, we will examine the likelihood ratio test, the *F* test, and *R*-square values for goodness of fit. The Pearson residual will detect outliers. Cook's distance will detect influential points, and leverage will detect problematic covariate patterns. The variance inflation factor will check for multicollinearity. The residual plots and interaction terms will check for linearity and additivity assumptions.

1.5.10.2 Data Analysis Aim 2.

We will use dual GBTM statistical methods to longitudinally examine the relationship of each symptom trajectory with the anastrozole adherence trajectory. Dual GBTM can examine two dependent variable trajectories together (Nagin et al., 2018).

1.5.10.3 Data Analysis Aim 3.

We will test the genetic variation for candidate genes as a risk factor for group membership to the trajectory classes (Aim 1, 2). We will use a multivariable regression model for Aim 1 and 2 trajectories to examine the role of candidate genes as predictors of class membership. If the subsample of 122 are not randomly distributed among the trajectory classes, we will conduct a new trajectory model for the subsample. If the subsample of 122 are randomly distributed among the Aim 1 and 2 trajectory classes, we will conduct binary logistic regression (multinomial regression if more than two classes) using the genetic predictors without non-genetic predictors. If our groups are large enough, we will then conduct a logistic regression with genetic predictors while controlling for significant non-genetic predictors from previous models.

1.5.11 Potential Problems and Alternative Approaches

The existing data characterize the experience of AI therapy for women with breast cancer. However, the data were not collected for this study's purpose. Thus, there are variables that influence symptoms and adherence that were not assessed, e.g., personality traits.

We chose GBTM for translational purposes. Knowledge of critical times when adherence decreases can be used in practice immediately by simply following up with patients. This type of information could not be derived from a generalized linear mixed model nor from a logistic regression. However, we will use an alternate method such as mixed linear regression repeated measures methods to evaluate patterns of adherence and symptoms if GBTM is not informative. Additionally, if logistic or multinomial regression to assess predictors of group membership is not feasible, we could assess risk factors (predictors) by entering the variables as risk factors into the trajectory modeling.

1.5.12 Protection of Human Subjects

The parent studies were reviewed and approved by the University of Pittsburgh Human Research Protection Office (IRB). Informed consent was obtained upon entry into the studies. This project has also received IRB approval (STUDY19050318; see appendices). All data are kept separate from participant identifiers. Names and other personal health information are kept in a separate locked cabinet. Data files are labeled with identification numbers in place of names. The applicant will not have any access to the names. All computers are kept behind the University of Pittsburgh firewall and are password protected and encrypted if required. Computers are also located in a locked office. All research personnel have completed the research training required by

the IRB and the Collaborative Institutional Training Initiative. Module certificates are updated every 1 to 4 years. There is minimal risk, no more than that of everyday life, to participants in this study, nor will they receive any benefit.

2.0 Summary of Results for Study

2.1 Summary of Main Results, Remaining Gaps, and Future Directions for Aim 1

Aim 1. Identify distinct subgroups of women based on self-reported symptoms trajectories and anastrozole adherence trajectories over the first 18 months of therapy.

2.1.1 Main Results

2.1.1.1 Neuropsychological Symptom Burden (NSB) Trajectories (N=360)

We found five distinct trajectories of neuropsychological symptom burden (NSB)—low-stable, low-increasing, moderate-stable, high-stable, and high-increasing, in a sample of 360 postmenopausal women (manuscript section 3.0 and shown below in figure 6). Pre-anastrozole NSB trajectories remained stable for three groups and had gradual increases in two groups. Indeed, as we increased the number of groups. per model and examined each "best-fitting" model, consistent trajectory shapes (intercept and linear) were identified. However, these trajectories show that a small group of women struggle with higher NSB, beginning at pre-anastrozole. Though we did not meet the conventional cut point for group size (5%) in the high/increasing group (4.1%), the five-group model provided a more meaningful description of the patterns of NSB than the three-group model. It remains to be seen if these results are clinically significant. Our composite score limits direct translation into practice. However, until translational tools for clinical practice are developed, nurses can be vigilant for these types of symptoms in their patients.

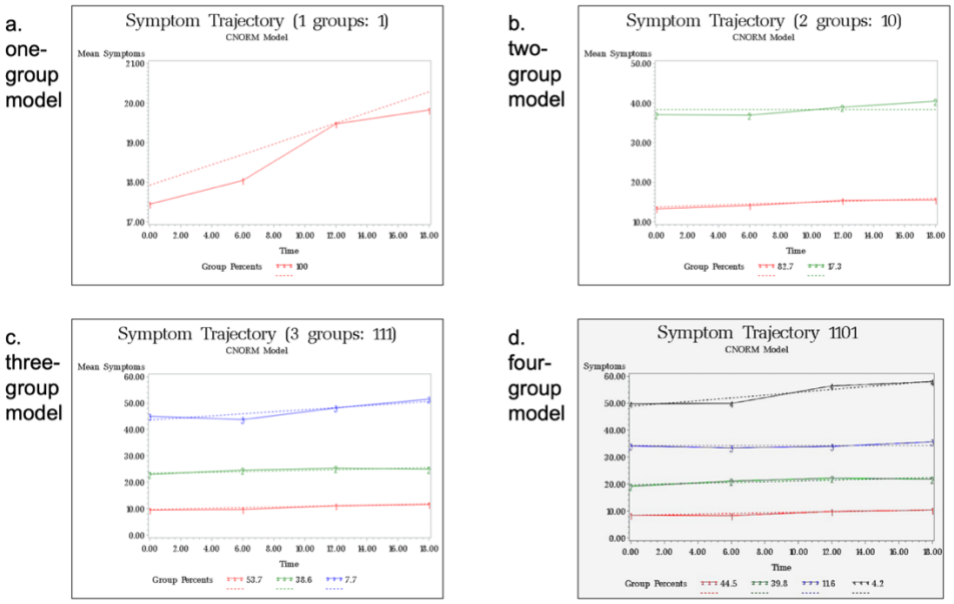


Figure 5 Neuropsychological Symptom Burden (NSB) Trajectory Models for One- through Four-groups

(see also manuscript 3.0 appendix A supplementary figure)

Note: Time points: pre anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; CNORM= censored normal; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 10= linear, intercept.

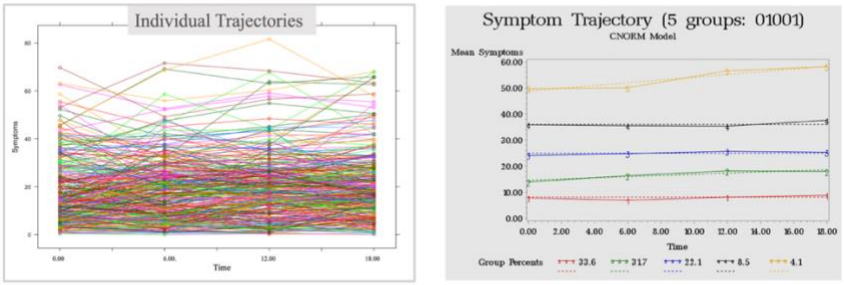


Figure 6 Individual Trajectories and 5-group NSB Model

(see also manuscript 3.0 appendix A figures)

Note: Time points: pre anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; CNORM= censored normal; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 01001= intercept, linear, intercept, intercept, linear.

[a]Individual trajectories were graphed using RStudio Version 1.4.1106 © 2009-2021 RStudio, PBC "Tiger Daylily" (2389bc24, 2021-02-11) for macOS

2.1.1.2 Anastrozole Adherence Trajectories (N=291)

In postmenopausal women with anastrozole adherence data, we found five distinct trajectories of anastrozole adherence—very low, low, high/sharp decrease, high/slow decrease, and persistently high. The shapes of the low (red, figure 7) and persistently high adherence (gold, figure 7) were flat (intercept). The 'very low' trajectory shape was quadratic (green in figure 7). Two trajectory shapes were cubic: high/sharp decrease and high/slow decrease (blue and black, respectively, in figure 7). Adherence dropped at or below 80% by five months post-initiation for more than one-third of the women.

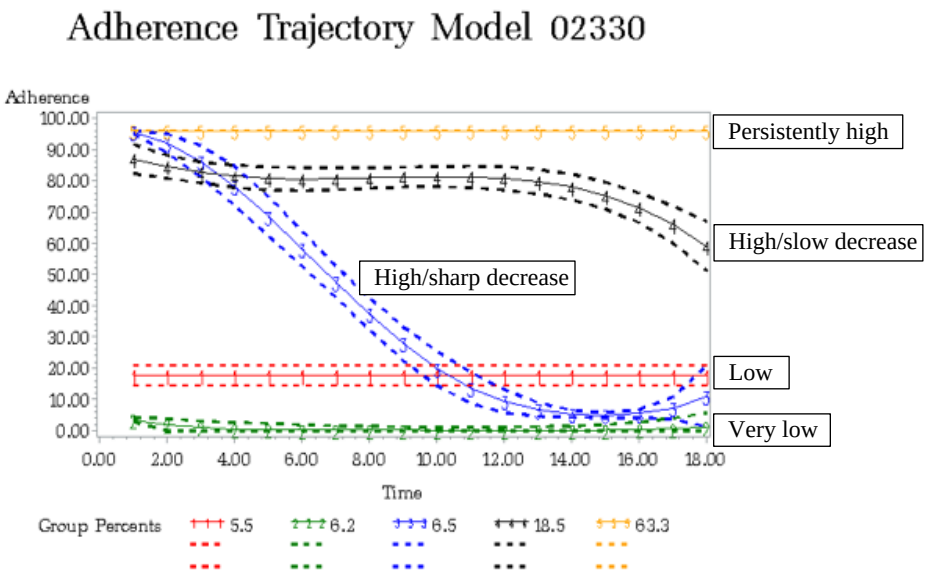


Figure 7 Anastrozole Adherence Trajectory Five-group Model

(see also manuscript 4.0 appendix C figures)

Note: anastrozole adherence trajectory image with confidence intervals. Time points every 2 months: e.g., pre-anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; censored normal model; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 02330= intercept, quadratic, cubic, cubic, intercept.

To summarize, most women in this sample were adherent to anastrozole. However, over one-third of this sample had suboptimal adherence early in the treatment course (all except the persistently high group). This study suggests that women may benefit from adherence interventions before and/or early in their therapy.

2.1.2 Remaining Gaps and Future Directions Symptoms and Anastrozole Adherence

Gaps remain in assessing symptom burden over time. It is unclear whether the trajectories of other symptom clusters are similar to the neuropsychological symptom burden (NSB) patterns identified in this study. Further, elucidation of the patterns of co-occurring symptoms or symptom clusters and their relationship to adherence is needed.

The adherence trajectories showed good adherence for a large proportion of this sample. However, adherence decreased for one-third of the sample over time. Though the MEMS® is the single best available method of measuring adherence, our approach of removing self-reported non-use days in our analysis may have been biased toward adherence. As recommended, future research should include more than one approach to adherence measurement, for example, using an objective and subjective measure, e.g., MEMS® and a self-report measure, or using two objective measures, e.g., medication possession ratio and pill count (Gritz et al., 1989; Lam & Fresco, 2015; Park et al., 2015).

A significant gap remains for study of the nearly 30% of women who do not fill their initial AI prescriptions and fail to initiate therapy (Bowles et al., 2012; Camacho et al., 2017). Researchers need to examine barriers to filling these initial prescriptions.

Adherence to any oral anti-cancer agent is crucial. As more orally-delivered cancer therapy options become available, nurses are at the frontline of assessing and ensuring optimal initiation and adherence to these lifesaving medications.

2.2 Summary of Main Results, Remaining Gaps, and Future Directions for Aim 2

Aim 2. Identify distinct subgroups of women based on combined symptom and anastrozole adherence trajectories.

2.2.1 Main Results

To conduct dual symptom-adherence trajectory analysis, our participants needed to have NSB and adherence data. Thus, we re-evaluated the neuropsychological symptom burden (NSB) in the sample of 291 women for whom we had NSB and adherence data to prepare for the dual analysis. We found results similar to the larger sample. Three trajectories, low/stable, moderate/stable, and moderate-/increasing, showed that pre-anastrozole neuropsychological symptom burden generally remains stable for most women after anastrozole initiation. The trajectories are shown in figure 8 below.

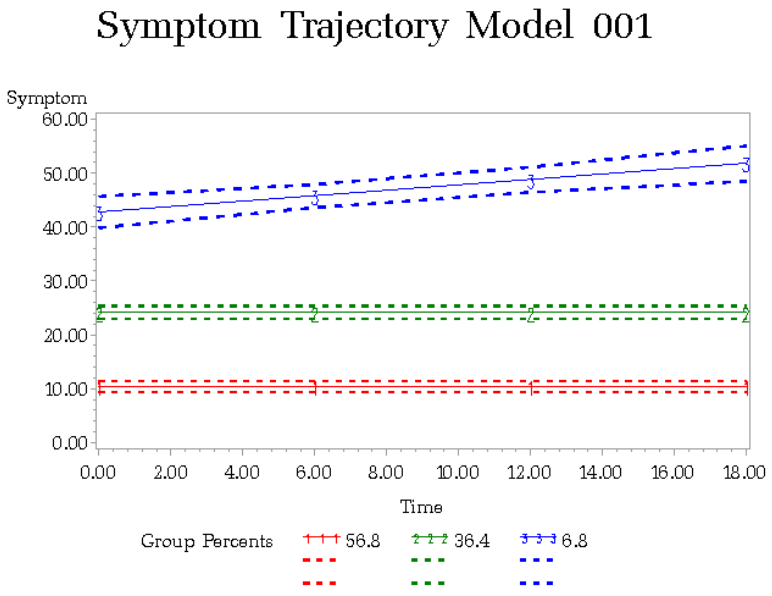


Figure 8 Neuropsychological Symptom Burden (NSB) Trajectory Three-group Model in Preparation for Dual Trajectory Analysis (N=291) **Neuropsychological Symptom Burden (NSB)**

Note: pre-anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; censored normal model; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 001= intercept, intercept, linear.

Dual trajectory analysis (five-group anastrozole adherence given three-group neuropsychological symptom burden models) revealed the highest probability (.736) for persistently high adherence given low/stable NSB. These results suggest that women whose NSB is low and stable are more likely to be adherent to anastrozole therapy. Women in the low/stable NSB group were most likely to be in the persistently high adherence group and much less likely to be in the low/decrease (.072) or high/decrease adherence (.065) groups. However, we found that for moderate/stable (.518) and moderate/increasing (.424) NSB, the probabilities of being in the persistently high adherence group are also greater. For the high/slow decrease adherence group NSB trended upward, suggesting that for some women, greater NSB *may* be associated with poorer anastrozole adherence.

NSB given adherence (Table 10, A2) showed that the highest probability (.662) was in the low/stable NSB group given the persistently high adherence group. This suggests that adherence does not increase NSB for this group. Further, women in the persistently high adherence group were much more likely to be in the low/stable NSB group than women the moderate/stable (.293) and moderate/increasing (.044) groups. This suggests that adherence to anastrozole may not be associated with *increased* NSB for most women.

The joint trajectory examines trajectory groups from NSB and adherence together. Again, the greatest probability (.424) is for women being in both the low/stable NSB and persistently high adherence groups.

Taken together, this suggests a bidirectional relationship (symptoms affecting adherence, adherence affecting symptoms).

Table 10 Dual NSB and Anastrozole Adherence Trajectory Results**Dual NSB and Anastrozole Adherence Trajectory Results**

Panel A. Dual Trajectory Adherence Given Neuropsychological Symptom Burden (NSB)

A.1. Probability of adherence group conditional on NSB group
**impact of NSB on adherence*

	NSB Trajectory Group		
Adherence Trajectory Group	Low/stable	Moderate/stable	Moderate/increasing
Very low	.029	.088	.103
Low	.051	.071	.102
High/sharp decrease	.057	.069	0
High/slow decrease	.127	.254	.371
Persistently high	**.736**	**.518**	**.424**

A.2. Probability of NSB group conditional on adherence group
**impact of adherence on NSB*

	Adherence Trajectory Group				
NSB Trajectory Group	Very low	Low	High/ sharp decrease	High/ slow decrease	Persistently high
Low/stable	.295	.470	.563	.365	**.662**
Moderate/stable	.580	. 419	.437	. 50	**.293**
Moderate/increasing	.126	. 112	0	.135	**.044**

A.3. Joint probability of NSB and adherence groups

	Adherence Trajectory Group				
NSB Trajectory Group	Very Low	Low	High/ sharp decrease	High/ slow decrease	Persistently high
Low/stable	.016	.029	.032	.067	**.424**
Moderate/stable	.032	.026	.025	.092	.188
Moderate/increasing	.007	.007	0	.025	.029

2.2.2 Remaining Gaps and Future Directions

While low neuropsychological symptom burden at pre-anastrozole is related to persistently high adherence in dual trajectory analysis and higher adherence did not appear to be associated with increased NSB, there were some women who struggled with suboptimal adherence and for whom symptom burden trended higher. This potential relationship should be investigated further. In addition, it will be important to identify the phenotypic and biological factors that are associated with membership in women with suboptimal adherence and high symptom burden.

2.3 Summary of Main Results, Remaining Gaps, and Future Directions for Aim 3

Aim 3. Explore whether genotypic factors (e.g., germline, or heritable, genomic variation associated with anastrozole ADME pathway) and phenotypic factors (e.g., demographic, clinical) are associated with predicted group membership for a) *symptom trajectories,* b) *adherence trajectories, and* c) *the relationship between symptom and adherence trajectories together.*

2.3.1 Main Results

We found five NSB trajectories in the larger sample (N=360). We found three NSB trajectories in the sample of 291 women with NSB plus adherence data for the dual trajectory analysis. Described below we found three NSB trajectories for a sample of 122 women who had NSB, adherence, and genotypic data. The shapes of trajectory models among the different sample sizes were comparable (intercept, linear).

2.3.1.1 Phenotypic Predictors of NSB Trajectory Group Membership

Potential phenotypic predictors (Table 11, also Appendix A) were screened before entry into the multinomial regression analysis. Age and use of certain baseline (pre-anastrozole) medication categories were significant ($p<.05$).

Table 11 Patient and Clinical Characteristics Comparisons with Initial Neuropsychological Symptom Burden (NSB) Trajectory Group Membership to Screen for Use in Regression (N=360)

Characteristic	*F* statistic	*p*-value
Age*	3.57	<.01
Education in years	1.47	.21
Number of medications at baseline	1.42	.22
Characteristic	**Pearson chi-square**	***p*-value**
Race, White	7.86	.09 FE
Married/living with partner, yes	7.08	.13 FE
Stage I BC, yes	7.34	.12FE
Chemotherapy, yes	6.29	.18FE
Received radiation therapy, yes	5.38	.20 FE
Initial surgery breast conserving & biopsy, yes	25.98	.17
Medication categories at baseline, yes		
Thyroid medications	1.28	.87FE
Gastrointestinal reflux medications	3.30	.51FE
Vitamin/mineral supplements	0.31	.99
Herbal supplements	5.24	.26FE
Anti-cholesterol medications	4.00	.41FE
Diabetes/insulin medications	4.36	.36 FE
Anti-depressants*	53.90	<.01FE
Non-narcotic analgesic*	12.90	.01
Narcotic analgesics*	18.71	<.01FE
Anti-anxiety*	16.63	<.01FE
Calcium/vitamin D supplements*	12.58	.014

**= statistical significance p<.05; ANOVA used for continuous variables, Chi-square for categorical; FE=Fisher's Exact; degrees of freedom=4*

For the initial (Aim 1) NSB trajectory analysis (N=360), we conducted a multinomial logistic regression to assess for phenotypic predictors of five-group trajectory membership. Younger age (all higher NSB trajectories) and baseline medication use at pre-anastrozole, including anti-depressant use (all higher NSB trajectories), non-narcotic analgesic use (moderate/stable NSB), narcotic analgesic use (all higher trajectories), anti-anxiety use (high/stable NSB), and no calcium/vitamin D use (high/increasing NSB) predicted the NSB trajectories (section 3.0 and Appendix A).

Table 12 Patient and Clinical Characteristics Comparisons with Second Neuropsychological Symptom Burden (NSB) Trajectory Group Membership to Screen for Risk Factors in Modeling (N=291)

Characteristic	*F* statistic	*p*-value
Age*	4.68	.01
Education in years	1.38	.25
Number of medications at baseline	1.24	.11
Characteristic	Pearson chi-square	*p*-value
Race, White	4.76	.08 FE
Married/living with partner, yes	3.61	.16
Stage I BC, yes	3.78	.15
Chemotherapy, yes	4.63	.10
Received radiation therapy, yes	1.67	.43
Initial surgery breast conserving & biopsy, yes	1.62	.44
Medication categories at baseline, yes		
Thyroid medications	1.14	.58FE
Gastrointestinal reflux medications	0.74	.67FE
Vitamin/mineral supplements	0.13	.94
Herbal supplements	.86	.65
Anti-cholesterol medications	2.10	.35
Diabetes/insulin medications	1.19	.51 FE
Anti-depressants*	26.55	<.01FE
Non-narcotic analgesic	2.57	.28
Narcotic analgesics*	10.96	<.01FE
Anti-anxiety	3.96	.11FE
Calcium/vitamin D supplements*	8.24	.016

**= statistical significance p<.05; ANOVA used for continuous variables, Chi-square for categorical; FE=Fisher's Exact; degrees of freedom=2*

For the sample of 291 women, we screened for potential risk factors for the symptom trajectory membership (Table 12). We entered potential phenotypic predictors as risk factors into the trajectory analyses. In the NSB three-group model, phenotypic risk factors for higher NSB groups were similar. Younger age was a factor for group membership in the two higher NSB trajectories (moderate/stable, and moderate/increasing. Others have found younger age as a factor for greater NSB (Rosenberg et al., 2015). Baseline antidepressant use was a risk factor for moderate/stable and moderate/increasing groups. Perhaps women who reported depressive symptoms were being treated for them. Of note, antidepressants may be prescribed to treat other symptoms than NSB, for example sleep and certain types of pain (Everitt et al., 2018; Sansone & Sansone, 2008). Non-use of calcium & vitamin D was a risk factor for the moderate/increasing group membership. Vitamin D levels and NSB, especially cognitive function, have been associated

(Di Somma et al., 2017). Baseline narcotic analgesic use was a risk factor for the moderate/stable and moderate/increasing group membership. It may be that women have co-occurring pain, or this finding could be related to cognitive function measured by NSB (Cherrier et al., 2009) but opioid prescribing practices have changed in the years since these data were collected.

2.3.1.2 Phenotypic Predictors of Adherence Trajectory Group Membership

For the sample of 291 women, we screened for potential risk factors for the adherence trajectory membership (Table 13). We entered potential phenotypic predictors as risk factors into the adherence trajectory analyses. For the anastrozole adherence trajectory analysis (N=291), not using thyroid medication was a factor for the high/slow decrease adherence group membership and not using antidepressants was a trending factor for the persistently high adherence group membership.

Table 13 Participant Characteristics at Pre-anastrozole (N=291) for Adherence Trajectory Groups

Baseline Characteristics	Total Sample	Adherence Trajectory Group				
		Very Low	Low	High/ Sharp Decrease	High/ Slow Decrease	Persistently High
		Mean ± SD or N (%)				
Age (years) Range (years)	60.9 ± 6.4 40-75	61.4 ± 5.1 51-74	60.8 ± 6.2 49-72	60.9 ± 4.2 53-68	60.9 ± 6.8 44-75	60.7 ± 6.6 40-74
Education (years) Range (years)	14.8 ± 2.6 9-22	14.6 ± 2.3 9-18	15.7 ± 2.3 12-18	14.5 ± 2.9 12-21	14.8 ± 2.7 10-22	14.9 ± 2.8 11-22
Race White Black More than 1 race	 282 (97) 8 (2.7) 1 (0.3)	 33 (11.7) 0 (0) 0 (0)	 23 (8.2) 1 (12.5) 0 (0)	 11 (3.9) 0 (0) 0 (0)	 130 (46.1) 5 (62.5) 0 (0)	 85 (30.1) 2 (25.0) 1 (100)
Marital status, married or living with partner	197 (67.7)	25 (12.7)	14 (7.1)	9 (4.6)	86 (43.7)	63 (32.0)
Cancer Stage Stage I Stage IIa Stage IIb Stage IIIa	 191 (65.6) 54 (18.6) 22 (7.6) 15 (5.2)	 23 (12.0) 7 (13.0) 1 (4.5) 1 (6.7)	 20 (10.5) 3 (5.6) 0 (0) 1 (6.7)	 6 (3.1) 3 (5.6) 0 (0) 2 (13.3)	 84 (44.0) 27 (50.0) 11 (50.0) 8 (53.3)	 58 (30.4) 14 (25.9) 10 (45.5) 3 (20.0)
Received chemotherapy	89 (30.6)	7 (7.9)	4 (4.5)	3 (3.4)	49 (38.3)	26 (31.0)
Received radiation therapy	215 (59.7)	28 (84.8)	18 (75.0)	8 (72.7)	96 (71.1)	65 (73.9)

Initial surgery Breast conserving & biopsy	189 (52.5)	25 (75.8)	16 (66.7)	7 (63.6)	84 (62.2)	57 (64.8)
Number of baseline medications Range	6.1 (3.5) 0-16	7.1 ± 4 4 0-16	6.4 ± 3.7 0-16	5.7 ± 3.0 1-10	5.8 ± 3.4 0-16	6.1 ± 3.4 0-16
Baseline Medication Regimen Categories						
Non-narcotic analgesics	104 (35.7)	10 (9.6)	13 (12.5)	5 (4.8)	48 (46.2)	28 (26.9)
Narcotic analgesics	29 (10.0)	4 (13.8)	3 (10.3)	1 (3.4)	16 (55.2)	5 (17.2)
Calcium/vitamin D supplements	146 (50.2)	17 (11.6)	12 (8.2)	6 (4.1)	62 (42.5)	49 (58.3)
Antidepressants*	50 (17.2)	12 (24.0)	5 (10.0)	1 (2.0)	24 (48.0)	8 (16.0)
Thyroid*	53 (18.2)	13 (24.5)	3 (5.7)	1 (1.9)	20 (37.7)	16 (30.2)
Gastrointestinal reflux	60 (20.6)	11 (18.3)	6 (10.0)	3 (5.0)	24 (40.0)	16 (26.7)
Vitamin/mineral supplements	182 (62.5)	26 (14.3)	16 (8.8)	5 (2.7)	78 (42.9)	57 (31.3)
Herbal supplements	91 (31.3)	14 (15.4)	9 (9.9)	3 (3.3)	37 (40.7)	28 (30.8)
Cholesterol	80 (27.5)	7 (8.8)	6 (7.5)	6 (7.5)	35 (43.8)	26 32.5)
Diabetes/insulin	32 (11.0)	3 (9.4)	2 (6.3)	2 (6.3)	14 (43.8)	11 (34.4)
Anti-anxiety	25 (8.6)	5 (20.0)	2 (8.0)	2 (8.0)	7 (28.0)	9 (36.0)

**= statistical significance p<.05*

2.3.1.3 Phenotypic Predictors of Dual Trajectory Group Membership

Dual trajectory risk factor analysis in the sample of 291 women was limited due to the small samples in each of the 15 groups created. We attempted to enter the significant risk factors from the adherence (antidepressant and thyroid use) and NSB (use of antidepressants, narcotic analgesics, and calcium/vitamin D supplements) but the analyses failed. However, we were able to assess age as the dual trajectory risk factor and found that younger age continued to be associated with greater NSB.

Identification of risk factors of greater NSB and suboptimal adherence can lead to assessment parameters of women at high risk for greater NSB and suboptimal adherence as well as the development of interventions to reduce NSB and improve adherence in women with breast cancer.

2.3.1.4 Genotypic Predictors of NSB and Adherence Trajectory Membership

Prior to evaluating genotypic risk factors, the NSB, the adherence, and the dual trajectory analyses were conducted for a third time using the reduced sample size (with NSB, adherence, and genomic data) (N=122), as shown in figures 9 and 10.

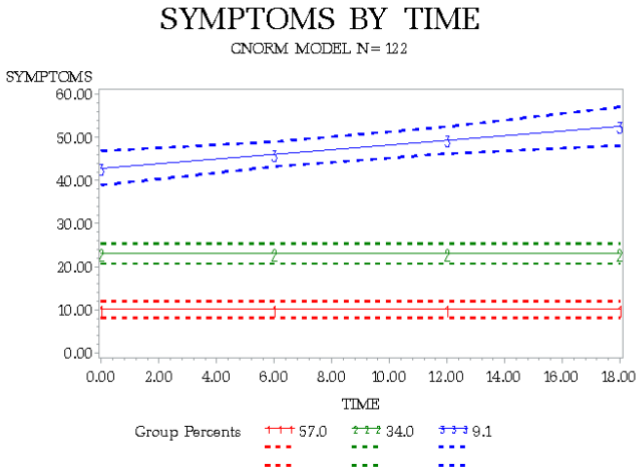


Figure 9 Neuropsychological Symptom Burden (NSB) Trajectory Three-group Model in Preparation for Dual Trajectory Analysis (N=122)

Note: pre-anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00

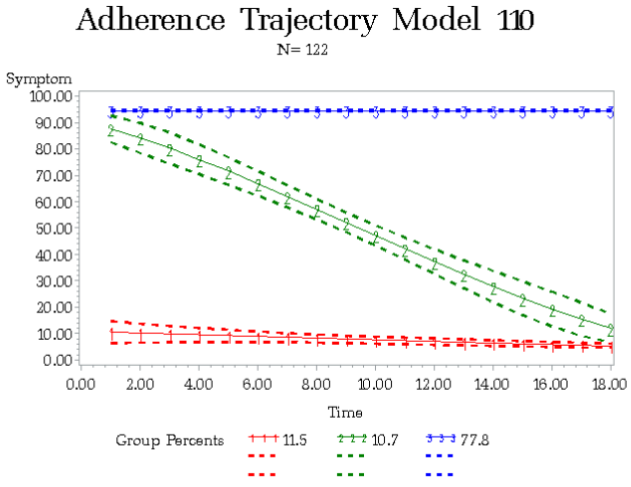


Figure 10 Adherence Trajectory Three-group Model in Preparation for Dual Trajectory Analysis (N=122)

Note: pre-anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00

The results for NSB, adherence, and dual trajectories are shown in Tables 14 and 15. Dual trajectory results for the smaller sample (N=122) were similar to dual trajectories in the larger sample.

Table 14 Neuropsychological Symptom Burden (NSB) and Adherence Trajectory Results with Genetic Predictors and Dual Symptom-Adherence Trajectories

NSB Trajectory 3-group Model BIC1= -1792.72 (N= 122) BIC2= -1797.57 (N= 488) AIC= -1782.91							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
001	1	b_0= 9.716	.570	.482, .658	.570	.950	14.482
	2	b_0= 23.039	.340	.256, .424	.344	.902	17.859
	3	b_0= 42.856 b_1= 0.538	.091	.040, .142	.090	.987	737.013

NSB with Genetic Risk Factors BIC1= -1711.16 (N= 116) BIC2= -1718.79 (N= 464) AIC= -1696.02				
Group	Parameter	Estimate	Standard Error	p-value
1	Baseline (reference)	(0)		
2	Constant	0.346	0.457	.449
	***ESR1* rs1884051**	**-1.108**	**0.491**	**.024**
	PGR rs471767	-0.484	0.490	.323
3	Constant	-3.95	1.366	.004
	ESR1 rs1884051	0.359	0.753	.634
	***PGR* rs471767**	**2.586**	**1.286**	**.045**

Adherence Trajectory 3-group Model BIC1= -4890.35 (N= 122) BIC2= -4901.43 (N= 1947) AIC= -4879.13							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
110	1	b_0= 4.582 b_1= -0.638	.115	.058, .172	.115	.999	>1 million
	2	b_0= 97.896 b_1= -5.079	.107	.052, .162	.107	.910	84.103
	3	b_0= 106.542	.778	.705, .852	.779	.998	134.554

Adherence with Genetic Risk Factors BIC1= -4387.14 (N= 106) BIC2= -4418.82 (N= 1688) AIC= -4360.50				
Group	Parameter	Estimate	Standard Error	p-value
1	Baseline (reference)	(0)		
2	Constant	-3.183	1.327	.017
	ESR1 rs6557171	3.051	2.671	.253
	ESR1 rs7761846	16.253	663.203	.980
	***ESR1* rs985694**	**3.178**	**1.464**	**.030**
	ESR1 rs2347867	-2.798	2.228	.209
	PGR rs1942836	1.519	1.303	.244
3	Constant	1.470	0.431	.001
	ESR1 rs6557171	-0.096	1.723	.956
	ESR1 rs7761846	13.033	633.202	.984
	ESR1 rs985694	0.616	0.806	.445

	ESR1 rs2347867 ***PGR* rs1942836**	0.543 **2.034**	1.632 **1.079**	.739 **.060**

Dual Adherence (3-group) given Symptom (3-group) Trajectory Model BIC1= -6689.89 (N= 122) BIC2= -6718.33 (N= 2435) AIC= -6663.26						
Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
1	b_0= 4.583 b_1= -0.638	.115	.058, .172	.115	.999	>1 million
2	b_0= 97.960 b_1= -5.084	.108	.053, .135	.108	.992	1,018.355
3	b_0= 106.546	.778	.704, .852	.778	.997	109.880

Table 15 Dual NSB and Anastrozole Adherence Trajectory Results in 122 Women with Genetic Data

Panel A. Dual Trajectory Adherence Given Neuropsychological Symptom Burden (NSB) N=122

A.1. Probability of adherence group conditional on NSB group *Impact of NSB on adherence*			
	NSB Trajectory Group		
Adherence Trajectory Group	Low/stable	Moderate/stable	Moderate/increasing
Low/decrease	.072	.167	.181
High/decrease	.065	.153	.199
Persistently high	**.863**	**.680**	**.621**

A.2. Probability of NSB group conditional on adherence group N=122 *Impact of adherence on NSB*			
	Adherence Trajectory Group		
NSB Trajectory Group	Low/decrease	High/decrease	Persistently high
Low/stable	.353	.338	**.624**
Moderate/stable	.503	.493	.303
Moderate/increasing	.144	.169	.073

A.3. Joint probability of NSB and adherence groups N=122			
	Adherence Trajectory Group		
NSB Trajectory Group	Low/decrease	High/decrease	Persistently high
Low/stable	.040	.036	**.485**
Moderate/stable	.058	.053	.236
Moderate/increasing	.017	.018	.057

Using a candidate gene approach, potential genotypic risk factors for trajectory group membership were selected based on function and associations found in literature. Table 16 shows the individual trajectory analyses including testing of genetic variation as risk factors for NSB or adherence trajectory group membership.

Table 16 Candidate Genes for Entry as Risk Factors of NSB and Adherence Trajectory Group Membership

Candidate Gene	SNV	Chi-square Fisher-Freeman-Halton Exact Test	*p*-value FE	Chi-square Fisher-Freeman-Halton Exact Test	*p*-value FE
CYP3A4 Cytochrome P450 Family 3 Subfamily A Member 4		Adherence Trajectory Groups		Symptom Trajectory Group	
*1G	rs2740574	.276	1.000	3.768	.102
*1G	rs2242480	1.433	.543	.354	.895
*22	rs35599367	3.687	.128	3.599	.189
CYP3A5 Cytochrome P450 Family 3 Subfamily A Member 5		Adherence Trajectory Groups		Symptom Trajectory Group	
*3	rs776746	.624	.833	1.582	.524
UGT1A4 UDP Glucuronosyltransferase Family 1 Member A4		Adherence Trajectory Groups		Symptom Trajectory Group	
*3a	rs3732219	1.281	.489	.460	.857
*3a	rs3732218	1.308	.481	.496	.854
*3a/b	rs2011425	1.258	.501	.493	.802
ESR1 *Estrogen Receptor 1 (alpha)*		Adherence Trajectory Groups		Symptom Trajectory Group	
rs10484919		.619	.801	.364	.928
rs1062577		.615	.783	.107	1.000
rs11964281		.570	.817	3.729	.134
rs12173570		2.326	.317	1.629	.454
rs12665044		.490	.783[a]	2.786	.257
rs1514348		2.111	.359	1.765	.374
rs1801132		3.606	.165[a]	.656	.724
rs1884051		3.507	.173[a]	*4.165	.125[a]
rs2046210		2.230	.328[a]	2.497	.335
rs2071454		1.310	.545	3.367	.156
rs2077647		2.975	.214	.923	.685
rs2228480		1.899	.413	.223	.959
rs2234693		4.448	.115	2.189	.324
rs2347867		**6.574**	**.037**	.418	.811
rs2744677		.150	1.000	.144	1.000
rs2813543		.351	.828	1.560	.448
rs2813544		1.133	.607	.836	.681
rs2941740		1.073	.636	3.770	.150
rs3020314		2.851	.240[a]	1.584	.453[a]
rs34535804		.593	.775	.775	.820

rs3778099	3.863	115	1.899	.375
rs3778609	1.350	.462	1.677	.363
rs3798577	.451	.887	2.032	.352
rs488133	2.090	.349	1.107	.613
rs532010	2.634	.292	2.263	.357
rs6557171	**9.686**	**.007**	.269	.874[a]
rs728524	.770	.677	.848	.634
rs77275268	.986	.587	1.954	.407
rs7761133	1.086	.638	1.068	.652
rs7761846	**10.062**	**.007**	2.064	.340
rs7766585	1.399	.445	1.722	.472
rs7767143	.586	.794	1.088	.617
rs827421	5.249	.067	.694	.735
rs851967	1.267	.531[a]	4.861	.089
rs851971	.920	.631[a]	4.216	.131
rs851982	.567	.759	1.330	.527
rs851998	1.112	.574[a]	5.032	.085
rs910416	1.034	.621	3.530	.170
rs9322331	1.690	.433	3.110	.214
rs9340799	2.007	.395	3.382	.186
rs9383938	1.040	.603	.412	.808
rs9397435	.497	.809	.422	.924
rs9397456	3.585	.159	.876	.690
rs9478245	.347	1.000	1.474	.666
rs985694	**6.171**	**.046**	1.755	.456
ESR2 *Estrogen Receptor 2 (beta)*	Adherence Trajectory Groups		Symptom Trajectory Group	
rs4986938	.370	.831	1.281	.542
PGR *Progesterone Receptor*	Adherence Trajectory Groups		Symptom Trajectory Group	
rs1042838	3.662	.155	.537	.842
rs1042839	3.497	.170	.292	.936
rs10895068	2.155	.264	.353	.913
rs11224561	2.473	.284	2.537	.287
rs1893505	1.041	.594[a]	1.195	.533
rs1942836	**6.366**	**.039**	1.496	.455
rs471767	.805	.732	**8.117**	**.017**
rs474320	5.159	.068	.628	.788
rs4754732	.106	1.000	1.351	.578
rs484389	4.532	.098	1.295	.546

rs568157	.894	.691	1.503	.485
rs590688	1.183	.581	2.654	.250
rs608995	4.565	.098	1.598	.476

*[a]asymptotic chi-square result; *entered into this analysis, bold significant p<.05*

Genomic samples were collected via (1) blood or (2) saliva. The sample was logged in, centrifuged, and white cells removed. DNA extracted from white cells used a simple salting out procedure (Miller et al., 1988). (2) Saliva collection used the Oragene™ DNA self-collection kit from DNA Genotek Corporation. Product protocol and reagents for extraction in the Oragene™ kit were followed. DNA was stored in 1X TE buffer at 4°C. Within 48 hours of collection, samples were processed, DNA extracted, aliquoted, diluted, and placed in a -80°C freezer for banking. Either the iPLEX® Agena Bioscience MassARRAY® platform for genotyping (Ellis & Ong, 2016) or PCR and gel electrophoresis will be used.

Four single nucleotide variants (SNVs) for *CYP3A4*, five SNVs for *CYP3A5*, three SNVs for *UGT1A4*, 49 for *ESR1*, one SNV for *ESR2*, and 13 SNVs for *PGR* were tested. SNVs with only one allele (*CYP3A4* rs28371759, rs55965422, *CYP3A5* rs28365083, rs28383479 and rs56411402, *ESR1* rs1048919, rs8179176) or low call rates were not included in the analysis. SNVs were assessed for Hardy Weinberg Equilibrium (HWE). Due to the exploratory nature of Aim 3, no corrections for multiple testing were employed for any procedures.

Prior to entry as risk factors, we used the X^2 test of independence to assess for possible association of dichotomized genotype (both major allele versus one or both minor alleles) and trajectory group membership.

The variants screened that were associated with adherence trajectories included: *ESR1* rs6557171, rs7761846, rs985694, rs2347867, and *PGR* rs1942836. Only two variants were associated with NSB trajectories: *ESR1* rs1884051 and *PGR* rs471767. Of note, *ESR1*rs1884051 was significant in a previous preparation for NSB trajectory group-SNV analysis; therefore, we

entered it into this analysis. Thus, genotypic risk factors included single nucleotide variants for *ESR1* and *PGR.*

ESR1 rs985694 minor allele T (CC vs CT/TT) was a risk factor for being in the high/decrease adherence trajectory group. *PGR* rs1942836 minor allele C (TT vs CT/CC) trended as a risk factor for membership in the persistently high adherence trajectory group. *Not having* the minor G allele for *ESR1* rs1884051 (AA vs AG/GG) was a factor associated with membership in the moderate/stable NSB trajectory group. While *PGR* rs471767 minor allele G (AA vs AG/GG) was a risk factor for the moderate/increasing NSB trajectory.

To summarize, for the candidate genes tested, four different SNVs of *ESR1* and *PGR* were associated with trajectory group membership for NSB (two) or adherence (two). These two genes are nuclear steroid hormone receptors that also play a role in transcription that increases protein synthesis and are involved in reproductive and bone health (Garrison, 2019). The literature is scant for these SNVs. The women in this study have estrogen receptor positive breast cancer so it may be that these variants are related to having breast cancer (Wu et al., 2020) but literature for these four SNVs does not show relationships to breast cancer. However, there is research to associate mutations of *ESR1* to endocrine therapy use (Najim et al., 2019).

ESR1 rs985694 was significantly associated with type 2 diabetes mellitus in European cohorts (Dahlman et al., 2008). Risk for breast cancer is increased in women with type 2 diabetes and type 2 diabetes is often associated with higher body mass index (BMI). A potential factor in symptom development is body mass index (BMI), which was not available in our sample (Wang et al., 2013).

PGR rs1942836 has been linked with pregnancy loss (Bahia et al., 2018) and preterm birth (Hackbarth et al., 2015; Kadivnik et al., 2022; Mann et al., 2013).

ESR1 rs1884051 was associated with vasopressin levels in Korean men, and the oxytocin-vasopressin pathway in response to infant crying (Rybicka et al., 2021). The C allele was associated with hip fractures in a Chinese population (Wang et al., 2008) and in Caucasian females admitted to a hospital for hip fracture (Velasco et al., 2010). *ESR1* rs1884051 has also been linked to metabolic syndrome in a Mexican population (Cahua-Pablo et al., 2015). Metabolic syndrome has associations with poor cognitive function (Alcorn et al., 2019)and depression (Ghanei Gheshlagh et al., 2016).

PGR rs471767 is associated with endometrial cancer risk (Xu et al., 2009), fibroid classification in ovarian cancer (Kanabekova et al., 2022), and preterm birth (Langmia et al., 2015; Manuck et al., 2011).

In summarizing the scant literature existing for these four SNVs, the common threads are 1) BMI, metabolic syndrome, and type 2 diabetes, all of which are intertwined risk factors for breast cancer development 2) preterm birth, which may be suggesting hormone level changes; 3) fracture risk and bone density, which is often a problem with postmenopausal women taking endocrine therapy and is related to pain/arthralgias experienced by these women; and 4) other female gynecological cancer development.

2.3.2 Remaining Gaps and Future Directions

There are some limitations of our work related to the phenotypic and genotypic factors. We examined whether the use of baseline medications predicted NSB or adherence trajectory membership. The parent study data were collected in 2005-9 during the opioid epidemic; therefore, current narcotic prescribing practices would be changed. Moreover, the baseline medication regimen was self-reported and adherence to women's baseline (pre-anastrozole) medication

regimen was not measured. Consequently, to confirm whether these medications predicted NSB trajectories, additional research is needed to confirm these results in a sample reflecting current opioid prescription practices using valid and reliable measures of adherence to patients' baseline medication regimen. In addition, our sample was predominantly White and limited to postmenopausal women who were ≥ 75 years of age. Thus, our results may not be generalizable to a more diverse cohort, women over 75 years of age, patients with other cancers, or males, though our work provides a framework to study these additional populations.

Our sample size decreased as we combined neuropsychological symptom burden with anastrozole adherence dual trajectories, which resulted in 15 groups and limited our ability to assess risk factors for the dual analysis. Our sample size decreased even more for dual trajectories using genetic risk factors with 9 groups (N=122). Data from larger samples, combining data from multiple studies, is needed to confirm our results.

We used a candidate gene approach for the exploratory aim of this study. A limitation was that our sample size was small, and we did not correct for multiple testing. While we acknowledge this limitation, we want to emphasize the exploratory nature of this aim and the advantage of using data with thorough phenotyping. Indeed, a genome wide association study (GWAS) would be ideal to test all associations simultaneously, but it would be challenging to get a sufficiently-sized sample with well-characterized symptom and adherence phenotypes over time. Therefore, targeted functional candidate gene studies are the appropriate approach when quality existing data are available. Other omic approaches, e.g., epigenomics, may reveal changes to the genome that influence phenotypes. Prospectively-collected data from clinical settings may also be helpful to assess symptoms experienced by women. Regrettably, adherence is challenging and time-consuming to collect. Self-report in the clinical setting may be an option if combined with an

objective measure (MEMS® cap or medication possession ratio). Another approach is to pool data from multiple studies if data collected are comparable. Future studies should replicate results in a more diverse sample.

3.0 Data-based Manuscript: Trajectories of Neuropsychological Symptom Burden in Postmenopausal Women Prescribed Anastrozole for Early-Stage Breast Cancer

3.1 Abstract

Purpose: Aromatase inhibitors (AI) prolong survival for postmenopausal women with hormone receptor-positive breast cancer (HR+BC) but also burden patients with symptoms, a major reason for suboptimal AI adherence. This study characterizes inter-relationships among symptom measures; describes neuropsychological symptom burden trajectories and identifies trajectory group membership predictors for postmenopausal women prescribed anastrozole for HR+BC. **Methods:** This study utilized prospectively-collected data from a cohort study. Relationships among various self-reported symptom measures were examined followed by a factor analysis to reduce data redundancy before trajectory analysis. Four neuropsychological scales/subscales were rescaled (range 0-100) and averaged into a neuropsychological symptom burden (NSB) score, where higher scores indicated greater symptom burden. Group-based trajectory modeling characterized NSB trajectories. Trajectory group membership predictors were identified using multinomial logistic regression. **Results:** Women (N=360) averaged 61 years old, were mostly White, and diagnosed with stage I HR+BC. Several measures were correlated temporally but four neuropsychological measures had strong correlations and dimensional loadings. These four measures, combined for the composite NSB, averaged (mean ± standard deviation) 17.4±12.9, 18.0±12.7, 19.5±12.8, and 19.8±13.0 at pre-anastrozole, 6-, 12-, and 18-months post-initiation, respectively. However, the analysis revealed five NSB trajectories—low-stable, low-increasing, moderate-stable, high-stable, and high-increasing. Younger age and

baseline medication categories (pre-anastrozole), including anti-depressants, analgesics, anti-anxiety, and no calcium/vitamin D, predicted the higher NSB trajectories. **Conclusion:** This study found relationships among neuropsychological symptom measures and distinct trajectories of self-reported NSB with pre-anastrozole predictors. Identifying symptom trajectories and their predictors at pre-anastrozole may inform supportive care strategies via symptom management interventions to optimize adherence for women with HR+BC.

3.2 Introduction

One of eight women in the United States (US) will be diagnosed with breast cancer (BC) in their lifetime (Howlader et al., 2019). Most women are postmenopausal at diagnosis, and approximately 70% of tumors are hormone receptor positive breast cancers (HR+BC) (Howlader et al., 2018). The 5-year survival rate for early-stage female BC is approximately 90%. Consequently, US female BC survivors exceed 3.8 million (Miller et al., 2019).

Aromatase inhibitor (AI) therapy has played a major role in preventing recurrence and prolonging survival for postmenopausal women with early-stage HR+BC (Early Breast Cancer Trialists' Collaborative, 2015) by blocking peripheral estrogen production. Postmenopausally, ovarian estrogen production ceases, but aromatase (*CYP19A1*) continues to convert androgens to estrogens primarily through adipose tissue (Desta et al., 2009). Aromatase inhibition results in a precipitous drop in estrogens as the drug reaches steady state in 7 days (*Anastrozole*, 2021). While estrogen deprivation prevents disease recurrence, it is also associated with numerous bothersome symptoms (Marsden et al., 2019) that worsen AI adherence (Murphy et al., 2012; Sawesi et al., 2014).

Most women report *at least* one symptom associated with AI therapy (Aiello Bowles et al., 2012). These symptoms vary and include hot flashes, arthralgia/pain, mood changes, sleep disturbances, and sexual dysfunction, among others (*Anastrozole*, 2021). Each individual symptom may be bothersome, but they often co-occur (Li et al., 2020), resulting in a range of symptom phenotypes. Thus, symptoms vary inter-individually by type, severity, and prevalence (Beckwee et al., 2017; Zhu et al., 2019) or intra-individually (within the individual) over time (Kyvernitakis et al., 2014). These inter- and intra-individual differences in symptom phenotypes experienced by postmenopausal women with HR+BC make it challenging to study this phenomenon and determine appropriate symptom management interventions.

Despite extensive research into the relationship of AI symptom burden with treatment adherence, fully characterized AI-related symptom phenotypes remain understudied (Beckwee et al., 2017; Hershman et al., 2015; Lintermans et al., 2014). Conversely, evaluating all possible symptoms simultaneously and combining data for various symptom measures with differing measurement scores and disparate concepts can be challenging to manage for researchers and may increase burden for the participant. If, however, redundancy of measurement was identified (i.e., the same symptom being measured repeatedly using different instruments with no additional information obtained), then a more streamlined symptom battery could be used and participant burden could be reduced. Examining information for multiple symptom measures through utilization of data reduction strategies can mitigate some of these challenges when using previously collected data and may inform data collection for future studies.

Examination of the relationships among the many AI-related symptoms experienced by women and changes in symptoms over time addresses a significant knowledge gap and requires an assessment at pre-initiation of AIs. Knowledge of co-occurring symptoms will facilitate

supportive patient care and provide phenotypes to identify underlying biological pathways in the development of co-occurring symptoms, which may lead to precision healthcare to ameliorate symptoms. Fully characterizing symptoms will additionally lead to a better understanding of how symptoms might impact AI adherence. Studies have reported that the symptoms lead to switching therapies, poor quality of life, and suboptimal adherence and/or discontinuation of the therapy (Lintermans et al., 2014; Murphy et al., 2012; Sawesi et al., 2014; Wouters et al., 2014). AI therapy is recommended for at least five years, and addressing symptoms experienced may inform interventions to improve AI adherence, thereby maximizing survival benefits provided by the treatment (Sini et al., 2017).

While the significance of AI-related symptoms is established, most studies have summarized symptom scores at one (Aiello Bowles et al., 2012; Schover et al., 2014) or several timepoints (Kyvernitakis et al., 2014) for statistical analysis. While this approach has resulted in valuable information, summarized scores do not address information needed for personalized healthcare—an individual's experience over time. Group-based trajectory modeling is a way to examine longitudinal data prospectively without losing detail in the temporal symptom patterns that women experience and has been used to evaluate temporal changes for symptoms experienced by individuals with cancer (Merriman et al., 2010; Merriman et al., 2017). The strength of trajectory analysis is the ability to classify participants into groups by the shape of their response trajectory over time, graphing the course of the variable of interest, as a function of time, into distinct latent classes or trajectory groups (Nagin, 2014; Nagin & Odgers, 2010a). Therefore, trajectories examine the dynamic nature of self-reported symptoms (Nagin, 2014).

This study was carried out to examine symptom burden over time in women prescribed anastrozole for HR+BC. The purpose of this study was to (1) investigate the inter-relationship

among symptoms and reduce data redundancy and in preparation for trajectory analysis, (2) describe the trajectories of symptoms experienced by postmenopausal women with early-stage BC from before anastrozole initiation through the first 18 months post-initiation of therapy, and (3) identify phenotypic predictors for observed trajectory group membership.

3.3 Methods

3.3.1 Study Design, Sample, and Setting

This study is a secondary analysis using existing, prospectively-collected, longitudinal data from an observational parent study examining cognitive impairment and adherence in postmenopausal women prescribed anastrozole for early-stage HR+BC (Anastrozole Use in Menopausal Women R01CA107408, PI: Bender; Predictors of Adherence to Hormonal Therapy in Breast Cancer Oncology Nursing Foundation, PI: Bender). Participants were recruited for the parent study from multiple clinical sites at UPMC Hillman Cancer Center; details of that study were previously described (Bender et al., 2015). Briefly, enrollment criteria for the parent study were postmenopausal women ≤75 years of age; with a diagnosis of stage I-IIIa BC; post-breast cancer surgery with/without chemotherapy; able to speak and read English; and completed at least 8 years of education. Women from the parent study were included in this trajectory analysis if they 1) had symptom data and 2) were prescribed anastrozole as their AI therapy.

3.3.2 Informed consent

Informed consent and institutional review board approval were obtained by study personnel from the parent study prior to data collection. Additionally, the University of Pittsburgh Institutional Review Board approval was obtained for use of the parent study data for this study (STUDY19050318).

3.3.3 Measures

Herein we describe measures used to (1) examine relationships among the measures and preparation for data reduction and (2) describing trajectories for symptoms identified.

3.3.4 Correlations and Factor Analysis

Self-reported symptom data were collected at baseline (pre-anastrozole), and at 6-, 12-, and 18-months post-initiation of anastrozole. To assess the inter-relationship among symptoms experienced, we examined several self-report measures of symptoms associated with AI therapy, e.g., anastrozole (see Appendix A Supplementary Table 1). The parent study collected a comprehensive assessment of symptoms such as endocrine therapy-related symptoms using the Breast Cancer Prevention Trial Symptom Checklist (BCPT) (Stanton, 2005), pain severity/interference using the Brief Pain Inventory (BPI) (Daut et al., 1983), anxiety and fatigue using the Profile of Mood States (POMS) Tension/Anxiety and Fatigue/Inertia subscales (McNair et al., 1992), depressive symptoms using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), sleep disturbance using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and

Epworth Sleepiness Scale (Johns, 1991), and economic hardship using the Psychological Sense of Economic Hardship (Barrera et al., 2001).

To reduce dimensionality and redundancy, an exploratory factor analysis was conducted (refer to the analysis section for details), which lead to a reduction of the data for neuropsychological symptom measures—the BCPT cognitive subscale, POMS Tension/Anxiety and Fatigue/Inertia subscales, and BDI-II.

The BCPT (Ganz et al., 1995; Stanton, 2005; Terhorst et al., 2011) is a measure of the self-reported degree of bother for 42 hormone therapy- and menopausal-related symptoms experienced by women in the previous 4 weeks, using a 5-point Likert scale (0 = not at all to 4 = extremely) (Stanton, 2005). The measure includes eight subscales: vasomotor, gastrointestinal, bladder, gynecological, dyspareunia, musculoskeletal, cognitive (BCPT-cog), and weight problems (Terhorst et al., 2011). Subscale scores utilized for this analysis were derived from the subscales identified in a sample of women with BC (Terhorst et al., 2011). Cronbach's alphas for the cognitive subscale were .87 (at baseline) and .92 (6-months) in women with BC receiving hormonal therapy (Terhorst et al., 2011). The possible range for the BCPT-cog is 0-12, The measure provides descriptors like "forgetfulness" and "difficulty concentrating" over the past month.

The POMS (Norcross et al., 1984) Tension/Anxiety (POMS T/A) and Fatigue/Inertia (POMS F/I) subscales measure self-reported anxiety (9 items; possible range 0-36) and fatigue (7 items; possible range 0-28), respectively, in the past week. Items are adjectives, e.g., "panicky" or "nervous" for POMS T/A and "sluggish" or "weary" for POMS F/I, rated on a 5-point Likert scale (0="not at all" 4="extremely") yielding a summary score of item responses (McNair, 1992). Internal consistency and test-retest reliability are established (McNair, 1992).

The BDI-II (Beck et al., 1996) is a measure of 21 self-reported depressive symptoms and attitudes, which are ranked using a 4-point Likert scale of 0 to 3 and generate a total sum score ranging from 0 to 63 (Beck et al., 1996). A score of 19 or greater suggests a clinical diagnosis of depression. This measure has strong Cronbach alpha coefficients in different samples and correlates with the major depression episode portion of the Structured Clinical Interview for DSM-IV Axis I Disorders (.83) (Sprinkle et al., 2002).

3.3.5 Neuropsychological Symptom Trajectories

Data from the four neuropsychological symptom burden (NSB) measures were combined into a composite score for use in the trajectory analysis (details in analysis section). The NSB has a possible range 0-100. Higher scores indicate a greater symptom burden.

3.3.6 Phenotypic Predictors

Parent study personnel collected patient and clinical characteristics via participant self-report and/or medical record review such as sociodemographics, cancer stage, and current medications. Parent study research nurses assigned and coded medication categories. For the purposes of this report, we will refer to the category as baseline medication categories, presuming "use" for the baseline (pre-anastrozole) medications reported. This variable was self-reported, and adherence to their entire medication regimen was not measured.

3.3.7 Statistical Analysis

3.3.7.1 Correlation and Factor Analysis

We analyzed correlations among the measures to investigate the inter-relationship among symptoms. Subscales (e.g., BCPT, POMS) or total scores (e.g., BDI-II) for the measures were examined for a consistent moderate ($r = .3$ to $.499$) to strong ($r \geq .5$) Pearson correlation coefficients for each of the four timepoints (pre-anastrozole, 6-, 12-, and 18-months post-initiation; $p<.05$). The measures (subscales or total score) were entered into exploratory factor analyses (EFA) with varimax rotation to determine and confirm consistent dimensional loading (>.60) across the four time points. Cronbach's alpha for each time point were analyzed for the selected dimension.

Missing data were imputed for the neuropsychological measures using a multiple imputation command with linear regression in SPSS, set at the default of 5 imputations (IBM Corp. Released 2020. IBM SPSS Statistics for MacIntosh, Version 27.0. Armonk, NY: IBM Corp.).

Scores from the four neuropsychological measures were rescaled to a 0-100 score, combined, and averaged into a neuropsychological symptom burden score (NSB).

3.3.7.2 Neuropsychological Symptom Burden (NSB) Trajectory Analysis

NSB at pre-anastrozole, 6-, 12-, and 18-months post-therapy initiation were analyzed using group-based trajectory modeling (GBTM) (censored normal). Trajectories were generated using SAS software for Windows (Version 9.4 copyright © [2020] SAS Institute Inc. SAS Institute Inc., Cary, NC, USA) with PROC TRAJ for GBTM (Jones et al., 2001).

To accommodate and evaluate temporal pattern changes in symptoms, we utilized trajectory analysis for NSB and subsequently identified distinct groups of participants (Nagin &

Odgers, 2010a). We tested the polynomial order (intercept, linear, quadratic, cubic) for each trajectory group combination. Model fit was assessed using Bayesian information criteria (BIC) and estimated distinct latent class membership probabilities to choose the best fitting model. Larger BICs indicated a better model fit, and the target for average posterior probabilities was >70%. We established best trajectory groups for each model (1-, 2-, 3-, 4-, and 5-group). For the best fitting model, we conducted a multinomial logistic regression using phenotypic predictors, entered as main effects.

3.3.7.3 Phenotypic Predictors

Patient and clinical characteristics were examined as potential phenotypic predictors descriptively and for bivariate relationships among variables and trajectory groups. Characteristics that were significantly ($p<0.05$) associated to the trajectory groups were entered as predictors in the regression. Bootstrapping (simple, 1000 samples, bias-corrected and accelerated) was performed. Log likelihood and pseudo R-squared tests were assessed to account for correct group classifications. To further confirm findings, we also entered risk factors to check the robustness of the findings using the PROC TRAJ regression. Statistical significance was set at alpha<0.05. (See supplement for details on sample size).

3.4 Results

3.4.1 Participant Characteristics

These postmenopausal women (N=360) prescribed anastrozole for HR+BC were on average (±SD) 61 ± 6 years of age (median=60), mostly White (97%), married/living with partner (69%) highly educated (average years of education=15 ± 3, median=14), with Stage I HR+BC (67%) (Table 1).

3.4.1.1 Baseline Medication Regimen Categories at Pre-anastrozole

On average, women reported 6.0 ± 3.6 baseline medications (pre-anastrozole time point) (Table 1). Most women did not receive chemotherapy prior to initiating anastrozole for their HR+BC (69%).

3.4.2 Inter-relationship Among Symptom Measures

Operationalization, conceptualization, and measurements of symptoms varied based on the measure. To prevent redundance and reduce the data redundancy for the trajectory analysis, we used a data-driven approach by first examining correlations among symptom measures to assess for potential relationships. Correlation coefficients among the BDI-II, POMS T/A, POMS F/I, and BCPT-cog were moderate to strong over time (shown in Table 2). Supplementary Table 2 reports correlation strengths among all measures temporally. The sleep and economic hardship measures were removed from further analysis for poor variability and small sample size, which would have impeded the trajectory analysis.

To further evaluate the relationships among the measures, we conducted an exploratory factor analysis for all timepoints. Pain (BPI subscales and BCPT musculoskeletal subscale) consistently loaded on one dimension with the BCPT musculoskeletal subscale cross loading onto other dimensions. The variance explained improved when pain scales were removed. Neuropsychological symptom burden (NSB; Dimension 1) consistently loaded on one dimension for all timepoints throughout the analyses (Table 3). Several measures/subscales cross loaded at various timepoints, underscoring the relationship among these symptoms. For example, the BCPT vasomotor and bladder control subscales at 18-months cross loaded onto different dimensions. Thus, a forced 5-factor model with varimax rotation was chosen (Table 3), and the BDI-II, BCPT-cog, the POMS T/A, and the POMS F/I were selected for the symptom trajectory analysis. Scree plots are shown in Appendix A Supplementary Figure 1. Cronbach's alpha for the four measures at pre-anastrozole, 6-, 12-, and 18-months were .78, .82, .85, and .87, respectively. The results for the correlations and strong consistent loadings on the same dimension in factor analysis suggested that these measures could be combined into a meaningful composite score.

3.4.3 Neuropsychological Symptom Burden (NSB)

Mean scores for each of the four neuropsychological symptom measures were low at pre-anastrozole, increased at 6- and 12-months, then either increased (POMS T/A) or plateaued (BDI-II, POMS F/I, BCPT-cog) at 18-months post-anastrozole initiation. NSB tended to increase over time, with average±SD of 17.4±12.9, 18.0±12.7, 19.5±12.8, and 19.8±13.0 at pre-anastrozole, 6-, 12-, and 18-months post-initiation, respectively. These measures were combined to create the composite NSB (Supplementary Table 3).

3.4.3.1 Trajectories for NSB

The NSB was used for trajectory analysis. Individual trajectories were graphed (Appendix A Figure 1a). The 1-group trajectory results using the entire sample reflected findings of the means over time, in that the NSB increased with a linear order (Appendix A Supplementary Figure 2). The model we chose as best fitting and most informative for the NSB was the 5-group (Appendix A Figure 1b): low-stable with 33.6% of the sample, low-increasing with 31.7%, moderate-stable with 22.1%, high-stable with 8.5%, and high-increasing with 4.1% of the sample. Though high-increasing is less than 5%, the posterior probability and odds of correct classification are very high. Thus, pre-anastrozole NSB appears relatively unchanged temporally for three groups and increased slightly from pre-anastrozole for two groups. The overall average posterior probability was 90.4%. Trajectory fit and diagnostic results for 1-5 group models are in Table 4 and figures for the models 1-4 are in Supplementary Figure 2.

3.4.3.2 Predictors for NSB Trajectory Group Membership

Phenotypic patient and clinical characteristics were examined for possible associations with NSB trajectory group membership (Appendix A Supplementary Table 4). Race, marital status, stage of BC, education in years, number of medications taken at baseline (pre-anastrozole), and several baseline medications were *not* associated with the NSB trajectory group membership ($p \geq 0.05$). Medications used at baseline *not* associated with NSB trajectory group membership were thyroid medications, gastrointestinal reflux medications, vitamin/minerals supplements, herbal supplements, cholesterol medications, and diabetes/insulin medications. Age and certain medication categories were significantly associated with NSB trajectory group membership. Specific baseline medication categories that were associated with trajectory group membership ($p<0.05$) were anti-depressants, non-narcotic analgesics, narcotic analgesics, anti-anxiety

medications, and calcium/vitamin D supplements. Variables reaching statistical significance were selected for the regression analysis.

Based on multinomial logistic regression for the 5-group NSB trajectory analysis (Table 5), age and baseline (pre-anastrozole) medication categories (anti-depressants, non-narcotic analgesics, narcotic analgesics, calcium/vitamin D supplements) were predictors of trajectory group. Anti-anxiety medications trended as significant (p=0.06) in the model and were retained for prediction of the high-stable NSB trajectory group. The low-stable group was the reference, with older age and lack of use of certain baseline medication categories being associated with membership. Conversely, younger age was a predictor for the moderate-stable, high-stable, and high-increasing NSB trajectory groups.

Certain baseline medication categories predicted trajectories. Compared with the low-stable group, the three moderate and high NSB trajectory groups had increased odds of anti-depressant use. The high-increasing group had a wide confidence interval for anti-depressants most likely reflecting the small sample size, and it also had lower odds of taking calcium/vitamin D supplements. We conducted simple bootstrapping for the regression; confidence intervals are shown in Table 5. Bootstrap results confirmed the direction and/or significance for most regression results. Further evaluation using PROC TRAJ regression risk factor analysis confirmed the robustness of the findings with significant results in the same direction plus an additional finding of anti-anxiety use for the moderate-stable group (shown in Supplementary Table 5). The correct group classification for this model with phenotypic predictors was 40.8% overall, with the low-stable trajectory group having the greatest correct prediction rate of 72.5%.

3.5 Discussion

The purpose of this study was to examine relationships among common symptoms of anastrozole therapy, describe trajectories of the symptoms, and identify phenotypic predictors for the trajectories using existing data. There were temporal relationships among the symptom measures, which were especially strong for the neuropsychological symptoms. Five distinct trajectories from pre-anastrozole through 18-months post-initiation were characterized: low-stable, low-increasing, moderate-stable, high-stable, and high-increasing. Finally, predictors of trajectory group membership were identified, age and baseline medication categories.

3.5.1 Correlations and Factor Analysis

The self-reported symptom measures were often inter-related with moderate-strong correlations at various timepoints. These intricate relationships suggest the presence of temporally co-occurring symptoms, including sleep, pain, perceived economic hardship. Others have found multiple, co-occurring symptoms associated with poor quality of life and suboptimal AI adherence in postmenopausal women with HR+BC prescribed an AI (Lintermans et al., 2014; Murphy et al., 2012; Sawesi et al., 2014; Wouters et al., 2014).

We used a data reduction technique to decrease redundancy, which may inform future research on participant burden reduction. The correlation results showed a strong temporal relationship among neuropsychological symptoms (cognitive, fatigue, depressive, anxiety), which was confirmed with factor analysis. This type of symptom may affect a patient's experience of additional symptoms (Whisenant et al., 2019) and as well as their medication adherence (Dos Santos et al., 2019). We do not know if neuropsychological symptom trajectories are similar across

other types of symptoms, although our correlations over time with the measures considered for these analyses were moderately to strongly correlated at various timepoints. Marino et al. (2020) found a decrease in anxiety that reached significance and a nonsignificant decrease in depressive symptoms from pre-AI to 6-months in postmenopausal women with BC (Martino et al., 2020). A systematic review by Maass et al. (2015) found that women with BC have an increased risk for depressive symptoms for more than 5 years post diagnosis but not for anxiety (Maass et al., 2015). Thus, these neuropsychological symptoms may not be clinically actionable, but they indicate a constant underlying presence, beginning at pre-anastrozole through 18 months post-initiation. Future research on inter-relationships among symptoms over time is needed.

3.5.2 Neuropsychological Symptom Burden (NSB) Trajectories

Our trajectory analysis categorized five neuropsychological symptom burden patterns experienced over time (intra-individual variability) into inter-individual trajectory groups with various levels of symptom burden and little change over time, specifically, low-stable, low-increasing, moderate-stable, and two smaller groups for whom NSB was greater—high-stable and high-increasing. Our results are consistent with studies which have found distinct symptom trajectories utilizing similar statistical methods. For example, four trajectory groups were identified in women with BC during the first six months after surgery (Dunn et al., 2011) as well as cognitive symptoms (Bender et al., 2018; Merriman et al., 2017) and symptom clusters in patients with various types of cancer (Miaskowski et al., 2015). The neuropsychological symptom trajectories tended to start at various degrees for the *pre-anastrozole timepoint*, suggesting that future symptom management interventions may be focused prior to anastrozole initiation. Of note, none of the models suggested a sharp increase in NSB after anastrozole initiation. It may be that

these symptoms are consistently present regardless of anastrozole use. Though the high-increasing group size represented just 4.1% of the cohort, we elected to pursue the 5-group model, as the fit was better, the 4-group model had a similar group with lessor detail, and women with a high pre-anastrozole neuropsychological symptom burden with increasing symptoms are perhaps most at-risk for suboptimal adherence. Future studies should examine the role of anastrozole adherence trajectories and their interplay with symptom trajectories.

This study demonstrates the utility of trajectories by showing the difference between average scores at each timepoint and trajectories results. The individual trajectory, detailed information on intra-individual improvement or worsening of symptoms, is lost when using aggregated summary scores at discrete timepoints. For example, if we prospectively examine symptom scores, we will not know if symptoms for subgroups of women improve or worsen over time—it will only reveal *overall improvements or declines for the total sample*. A detailed phenotype using individual trajectories is more informative.

3.5.3 Phenotypic Predictors

The regression identified several phenotypic predictors of trajectory group membership. Similar to prior trajectory research, we found younger age to be associated with higher symptom burden (Merriman et al., 2010). However, medication categories have not been routinely examined as trajectory predictors. Baseline medication categories at the pre-anastrozole timepoint, specifically, anti-depressants, anti-anxiety medications, calcium/vitamin D, and non-narcotic and narcotic analgesics were predictors of trajectory group membership and verified with bootstrapping. One study found anti-depressant use was associated with switching endocrine therapies (Kemp-Casey et al., 2017). However, we do not know if the baseline medications

influence the neuropsychological symptom burden score through interactions between the medication and anastrozole or via side effects of anastrozole therapy and/or the medications. Alternatively, these symptoms may be a manifestation of the comorbid conditions which the medications treat. While baseline medication use (i.e., anti-depressants, analgesics) may simply be a predictor for NSB, unexplored pharmacologic or pharmacogenetic interactions (potentiation, inhibition) with anastrozole may also play a role. Future research should include potential pharmacologic and genomic predictors for anastrozole symptom development.

The study has some limitations. We reported on the five-trajectory model after we found meaningful trajectories in the smaller groups. If we had used the 5% cut point rule, we would have selected the 3-group model, thus we reported all models for transparency. We acknowledge that we exceeded the cut point for 5% in those groups, but the sample size could offset this limitation and the very high posterior probability and odds of correct classification were decisive. We do not know if these results are clinically actionable, though NSB may be consequential to the individuals. Sleep and economic hardship measures could not be used due to a smaller sample size. Future studies should examine the how these variables impact symptom burden in this population. The data were collected in 2005-9 amidst the advent of the opioid epidemic and may not reflect current narcotic prescribing practices. Baseline medication use was self-reported and adherence to that medication regimen was not measured. Thus, we do not know why these baseline medication categories were NSB predictors. We were unable to reliably determine the study participants' body mass index (BMI), which is also a potential symptom predictor (Wang et al., 2013). Future studies will need to address these gaps in the current science. Finally, these results may not be generalizable to a more diverse cohort, women over 75 years of age, patients with other cancers, or males, though our work provides a framework to study these additional populations.

3.5.4 Implications and Future Directions

Behavioral interventions as well as pharmacologic therapies may be helpful to mitigate neuropsychological symptoms and improve AI adherence. Identifying symptom trajectories is a first step to pinpointing timing for interventions. Characterizing patients at risk for a high symptom burden aids in targeting those who might benefit most from symptom management interventions. Our 5-group model suggests that neuropsychological symptoms vary at baseline (pre-anastrozole) with little temporal variation. The flat and slightly linear trajectory results suggest that early assessment and early intervention may ameliorate neuropsychological symptoms that are not clinically actionable. Future research should include characterizing adherence trajectories, the adherence-symptom relationship, and genomic factors.

Note: This manuscript was recently accepted for publication in *Supportive Care in Cancer*.

4.0 Data-based Manuscript: Anastrozole Adherence, Neuropsychological Symptom Burden, and Dual Adherence-Symptom Trajectories in Women with Early-Stage Breast Cancer

4.1 Abstract

Adherence to anastrozole prescribed for hormone receptor positive breast cancer (HR+BC) is often suboptimal. We aimed to characterize trajectories of anastrozole adherence from pre-anastrozole through 18 months post-initiation, identify risk factors for trajectory group membership, characterize co-occurring trajectories of adherence and neuropsychological symptom burden plus identify risk factors for group membership in postmenopausal women with HR+ BC.

Trajectory models for monthly (1-18) adherence scores and neuropsychological symptom burden (NSB) at pre-anastrozole, 6, 12, and 18 months were analyzed individually, and risk factors were evaluated for each model. The adherence and NSB models were entered into dual trajectory analyses, and risk factors were added.

In 291 women, we identified five distinct anastrozole adherence trajectories—very low (5.5%), low (6.2%), high/sharp decrease (6.5%), high/slow decrease (18.5%), and persistently high (63.3%). Adherence dropped at or below 80% by five months post-initiation for women in all groups (36.7%) except the persistently high group. We found three NSB trajectories— low/stable (58.8%), moderate/stable (36.4%), and moderate-/increasing (6.8%). Dual trajectories (5-group adherence given 3-group NSB models) revealed the highest probability (0.736) for persistently high adherence given low/stable symptoms. NSB given adherence yielded comparable results.

Anastrozole adherence was generally optimal in this sample, though one-third of women experienced decreases after treatment initiation. Taking anastrozole does *not* appear to increase NSB for most women. Results suggest women may benefit from adherence interventions before or soon after treatment begins. Dual trajectories suggest a *bidirectional relationship* between adherence and NSB. The results may guide future intervention development and timing.

4.2 Lay Summary

Postmenopausal women with hormone receptor positive breast cancer treated with anastrozole often experience bothersome symptoms that may be a barrier to taking the drug regularly (adherence). We found distinct patterns of symptom burden (for depression, anxiety, fatigue, cognition) and anastrozole adherence over the 18 months. Symptom burden remained stable from before anastrozole, except in 6.8% of women who had a slight increase. Most women took anastrozole regularly, but for one-third adherence dropped within five months. Taking anastrozole regularly does not seem to increase symptom burden for most women. But a higher symptom burden before starting anastrozole may impact adherence.

4.3 Introduction

In the United States, where one in eight women will face a breast cancer (BC) diagnosis in their lifetime, the most prevalent tumor type is hormone receptor positive (HR+) (Nadia Howlader et al., 2014; Howlader et al., 2021). Aromatase inhibitor (AI) therapy prescribed for at least five

years is standard for postmenopausal women with HR+BC. AI regimens *taken as prescribed* successfully prevent tumor recurrence, improving survival (Hershman et al., 2011; B. Makubate et al., 2013).

AI adherence, the extent to which a patient carries out their prescribed AI regimen, is suboptimal, despite the known clinical benefit of AIs. AI therapy adherence has been reported between 41-80%, decreasing with each year of therapy (B. Makubate et al., 2013; Murphy et al., 2012; Zhao et al., 2021). Medication adherence may be categorized into unintentional or intentional (Vrijens et al., 2012), but regardless of intent, disease- or treatment-related symptoms may be barriers to adhering (Sawesi et al., 2014).

AI-related symptoms are highly variable in severity and type and may include hot flashes, pain, anxiety, depression, cognitive problems, and more (Aiello Bowles et al., 2012; Wouters et al., 2014). Our team and others have found clusters of symptoms that were consistently correlated over time (Li et al., 2020; Miaskowski, 2016; Miaskowski et al., 2017). Suboptimal AI adherence has been associated with AI-related symptoms. Neuropsychological symptoms such as cognitive problems, depression, anxiety, and fatigue have been associated with both intentional and unintentional suboptimal adherence in patients with cancer (Dos Santos et al., 2019; Vardy et al., 2014; Wouters et al., 2014). Even baseline symptoms experienced before AI initiation have been associated with adherence (Sawesi et al., 2014; Wagner et al., 2018). Conversely, others have found that optimal adherence is associated with *fewer* symptoms over time (Kyvernitakis et al., 2014). Thus, it is possible that the relationship between symptoms and adherence is a bidirectional one—symptoms affect adherence and adherence affects symptoms.

Considering the known symptom variability among women prescribed AIs, the known relationship of neuropsychological symptoms and adherence in patients with cancer, and our

previous analysis with strong correlations among neuropsychological symptoms, we elucidated five distinct trajectories of neuropsychological symptom burden from pre-anastrozole through 18-months post-initiation in a sample of 360 postmenopausal women with HR+BC. However, to our knowledge, there has not been a temporal comparison of adherence *and* symptom trajectories, which is crucial knowledge for effective intervention development.

The purpose of this study is to (1) describe anastrozole adherence trajectories from anastrozole initiation through 18 months post-initiation, (2) identify phenotypic risk factors for the adherence trajectories, (3) elucidate the relationship between adherence trajectories *and* neuropsychological symptom burden trajectories by evaluating dual trajectories, and (4) characterize phenotypic risk factors for trajectories.

4.4 Methods

4.4.1 Study Design, Sample, and Setting

The current study is an analysis of prospectively-collected data from a parent study of postmenopausal women prescribed anastrozole for early-stage HR+BC (Anastrozole Use in Menopausal Women R01CA107408, PI: Bender; Predictors of Adherence to Hormonal Therapy in Breast Cancer Oncology Nursing Foundation, PI: Bender). Study personnel recruited parent study participants from multiple clinical sites at the UPMC Hillman Cancer Center. Methodological details of the parent study have been previously described (Bender et al., 2014; Bender et al., 2015). To be enrolled to the parent study, women were postmenopausal, 75 years of

age or younger; diagnosed with stage I-IIIa BC; post-BC surgery with/without chemotherapy; spoke and read English; and completed at least 8 years of education.

Women from the parent study were included in the trajectory analyses if 1) they had more than one month of adherence data assessed via electronic event monitoring (MEMS®), 2) they were prescribed anastrozole as their AI therapy, and 3) they had neuropsychological symptom burden data (McCall et al., accepted). The sample for this study included 291 women.

4.4.2 Informed Consent

The University of Pittsburgh Institutional Review Board approved the protocol for the parent study and for use of parent study data for this study (STUDY19050318). Prior to data collection, parent study personnel obtained informed consent from all participants.

4.4.3 Measures

Adherence data were collected continuously using an electronic event monitor (MEMS® cap, AARDEX Group SA), which time and date stamps cap openings. Electronic monitoring is known to be more accurate than many other methods, particularly self-report (El Alili et al., 2016). The participant was instructed to place her anastrozole into the pill container and take the medication as her physician prescribed. MEMS® cap data were downloaded at study visits (6, 12, and 18 months), during which the study personnel assessed use and questioned the participant about times she may not have used the cap, for example, during vacations (Bender et al., 2014). The responses were recorded and compared with the cap data. Any reported periods of non-use were not included in these analyses.

Given the 50-hour half-life of anastrozole (*Anastrozole*, 2021), the proportion of monthly anastrozole adherence (possible range 0-100), starting at anastrozole initiation was calculated using the following formula:

$$days\ with\ correct\ number\ of\ doses\ taken \div days\ prescribed$$

For example, anastrozole is prescribed once daily. If the participant took one dose *at any time that day*, it would be considered a "correct day". However, if she took no doses or more than one dose, that would be an "incorrect day". A cut point of <80% is considered suboptimal adherence (Murphy et al., 2012).

Neuropsychological symptom burden (NSB) was assessed with self-report measures at pre-anastrozole, and at 6 months, 12 months, and 18 months after initiation of anastrozole. NSB was derived from measures of depressive symptoms, anxiety, fatigue, and cognitive function, as previously described (McCall et al., accepted). Briefly, we conducted correlations for symptom measures of endocrine therapy-related symptoms (Ganz et al., 1995; Ganz et al., 2000; Stanton, 2005; Terhorst et al., 2011), pain (Atkinson et al., 2011), depression (Beck et al., 1996; Wang & Gorenstein, 2013), anxiety (Norcross et al., 1984), fatigue (Norcross et al., 1984), sleep (Buysse et al., 1989; Johns, 1991), and economic hardship (Barrera et al., 2001). We examined symptoms using factor analysis for the symptoms that were moderately or strongly correlated over time in a larger sample of 360 women. Neuropsychological symptom burden (cognitive problems, depression, anxiety, fatigue) strongly and consistently loaded onto one dimension via factor analysis at all timepoints. Thus, the Beck Depression Inventory (Beck et al., 1996; Wang & Gorenstein, 2013), the Breast Cancer Prevention Trial (BCPT) Symptom Checklist cognitive subscale (Ganz et al., 1995; Ganz et al., 2000; Stanton, 2005; Terhorst et al., 2011), and the Profile of Mood States (POMS) Tension/Anxiety and Fatigue/Inertia subscales (Norcross et al., 1984)

were rescaled and combined to form a composite score, the NSB. The possible range for NSB scores was 0-100, with higher scores indicating greater NSB.

Baseline patient characteristics were collected via self-report and clinical characteristics were derived from the medical record by parent study personnel, including women's self-reported medication regimen at baseline. Medication categories were assigned by the parent study's research nurses. We refer to the category as medication "use", while emphasizing that this was a self-report and adherence to the medication regimen was not measured.

4.5 Statistical Analysis

Data were summarized, analyzed descriptively, and assessed for relationships among variables and trajectory group membership.

4.5.1 Trajectory Analyses and Risk Factors

Monthly anastrozole adherence from 1- to 18-months post-therapy initiation, neuropsychological symptom burden (at pre-anastrozole, 6 months, 12 months, and 18 months post-initiation), and dual trajectories for adherence and neuropsychological burden were analyzed using group-based trajectory modeling (GBTM). SAS software for Windows (Version 9.4 copyright © [2020] SAS Institute Inc. SAS Institute Inc., Cary, NC, USA) with PROC TRAJ for GBTM (Jones et al., 2001) was used to conduct the trajectory analyses and generate results.

Trajectory analysis (GBTM) was utilized to assess temporal changes and trajectories in adherence. Distinct groups of participants were identified based on their adherence trajectories

(Nagin & Odgers, 2010a). The unique polynomial order (intercept, linear, quadratic, cubic) combination was tested for each trajectory model for one-group through five-group models. Models were screened for significance ($p<0.05$) for the highest order of each group. Bayesian information criterion (BIC), for sample (BIC1) and observations (BIC2) were used to select the best-fitting model, larger BICs indicated a better model fit. When BIC1 and BIC2 were largest for different models, models were evaluated by group size (>5% of the sample) and simplicity (simplicity score = #parameters + [5 * #groups in model]) (Heinsberg et al., 2020). Diagnostics for models were conducted. Average posterior probabilities were calculated and considered acceptable at >70%. Odds of correct classification were calculated; values were considered acceptable if >5. Other diagnostics such as estimated group proportion, actual group proportion, and confidence intervals were calculated. The best model for each number of groups (1-, 2-, 3-, 4- and 5-group) and overall were selected.

Pre-anastrozole (baseline) phenotypic risk factors (participant and clinical factors) were examined descriptively and screened for bivariate relationships with trajectory groups. Those associated with trajectory groups were entered as risk factors into the trajectory analysis. This process was repeated for the NSB trajectories. Though we previously analyzed NSB in a larger sample, we needed to re-analyze trajectories for the sample of 291, in preparation for the dual trajectory modeling.

4.5.2 Dual Trajectories and Risk Factors

The dual trajectory analysis was conducted in the same manner described above to compare trajectories of adherence with neuropsychological symptoms data. Risk factors were added to the GBTM to elucidate phenotypic risk factors of trajectory group membership.

4.6 Results

The sample was comprised of 291 postmenopausal women with early-stage HR+BC who were 60.9 years old on average, well-educated, predominantly White, and married or living with a partner. Less than one-third of the sample received chemotherapy. The average number of baseline medications was six. Most tumors were classified as stage I (Appendix B Table 6).

Anastrozole adherence, the proportion of monthly anastrozole adherence, averaged 86.96 ± 27.62 in the first month and gradually decreased, with some +/- fluctuations over time, to 77.28 ± 36.85 at 18-months. Symptom burden scores at pre-anastrozole averaged 16.86 ± 12.36. The symptom burden scores at 6, 12, and 18 months were 16.87 ± 12.56, 18.17 ± 12.66, and 18.60 ± 12.74, respectively.

4.6.1 Adherence Trajectories and Risk Factors

One-group through five-group models were explored for monthly adherence rates from initiation through 18 months post-initiation. Most four- and five-group models were not significant, and many of the models had small group sizes of <5%. Five-group had better fit, but model BICs did not agree and diagnostic testing results were comparable between two models: posterior probabilities (at least .90) OCC >5, estimated and actual group proportions and narrow confidence intervals and smallest group size of 5.51%. Therefore, most parsimonious model (02330) was chosen to represent the adherence in this sample with the following trajectories: very low (5.5%), low (6.2%), high/sharp decrease (6.5%), high/slow decrease (18.5%), and persistently high (63.3%) (see Appendix B Table 7, Panel A). Of note, the trajectories indicate that adherence

drops to 80% and below around 5-months for all groups except for the persistently high adherence group (Appendix B Figure 2).

After screening baseline patient and clinical characteristics for potential risk factors for trajectory group membership, baseline antidepressant use and baseline thyroid medication use were both significant, and, therefore, entered as risk factors into model 02330. Compared with the very low adherence group as reference, non-thyroid medication use was a statistically significant factor for the high/slow decrease group membership (b= -1.944; p= .02) and non-antidepressant use was a trending factor (p=.07) for the persistently high group membership (b= -1.089).

4.6.2 Neuropsychological Symptom Burden (NSB) Trajectories and Risk Factors

We tested one- through five-group models for the NSB in this sample. While the four- and five-group models had higher BICs, their smallest trajectory groups were <5% and removed from consideration. The three-group model 001 had the best fit and acceptable diagnostics with the following trajectory groups: 1) low/stable, 2) moderate/stable, and 3) moderate-/increasing symptom burden (Appendix B Table 7, Panel B; Figure 1. B.1. & 2.).

Four potential risk factors were entered into the model: age and self-reported baseline medication regimen categories—antidepressant use, calcium & vitamin D use, and narcotic analgesic use. Slightly younger age was a significant factor for membership in the moderate/stable NSB group (b= -0.068; p= .01) and a trend for the moderate/increasing group (b= -0.111; p= .06), compared with the low/stable group as reference. Baseline antidepressant use was a risk factor for membership in the moderate/stable group (b= 1.549; p= .0001) and the moderate/increasing group (b= 3.088; p= .0001). Non-use of calcium & vitamin D at baseline was a factor for moderate/increasing group membership (b= -2.994; p= .01). Baseline narcotic analgesic use

trended as a factor for moderate/stable group membership (b= 0.823; p= .09) and a significant factor for the moderate/increasing group membership (b= 2.645; p=.001).

4.6.3 Dual Trajectories: Adherence and Neuropsychological Symptom Burden (NSB)

Due to potentially bidirectional relationship between adherence and symptoms, dual trajectory modeling for adherence model 02230 and NSB model 001 was explored in both directions: 1) adherence given NSB and 2) NSB given adherence (Appendix B Table 8).

4.6.4 Dual Adherence Given NSB Trajectory and Risk Factors

For the dual adherence given NSB modeling, persistently high adherence given low/stable NSB had the highest probability of group membership at 0.736 (Appendix B Table 8, Panel A.1.). The persistently high adherence group given NSB shows that probabilities of group membership are greatest for the low/stable group, are lower (0.518) in the moderate/stable NSB group, and even lower (0.424) for the moderate/increasing NSB group. Joint probabilities also showed that the persistently high adherence group plus low/stable NSB group were highest of all groups at 0.424. Of note, the direction of the probability of membership in the high/slow decrease adherence group increased from the low to moderate/increasing NSB groups (0.127, 0.254, 0.371, respectively). This suggests that NSB may have some effect on this high/slow decrease adherence group. Diagnostics were within acceptable ranges for this model (Appendix B Table 7, Panel C). Trajectory images for the dual model and individual models are similar, with group proportions varying only slightly (Appendix B Figure 2).

4.6.5 Dual NSB Given Adherence Trajectory and Risk Factors

Dual trajectory modeling for NSB given adherence yielded similar results as shown in Table 3, Panels B.1-3. The low/stable symptom burden given persistently high adherence yielded the highest probability of all combinations at 0.662. Similar directions were observed for this analysis. Joint probabilities showed that low/stable symptom burden plus the persistently high adherence group was highest for all groups at 0.419. Diagnostics for this model were also within acceptable ranges (Appendix B Table 7, Panel D).

4.7 Discussion

This study examined trajectories for anastrozole adherence and neuropsychological symptom burden (NSB) and, to our knowledge, is the first to examine dual trajectories of adherence and NSB.

4.7.1 Anastrozole Trajectories and Risk Factors

Adherence to the prescribed regimen is associated with reduced disease recurrence and improved survival outcome, making adherence to the 5-year regimen crucial to receive treatment benefit (B. Makubate et al., 2013). We found that anastrozole adherence could be described using five distinct trajectories: very low, low, high/sharp decrease, high/slow decrease, and persistently high. Winn et al. (2019) analyzed medication possession ratios (MPRs) from claims data and reported six adherence trajectories. The researchers found a consistently high group (optimal

adherence) at 46.8% and other groups resembling some of our trajectories (Winn et al., 2019). Most women were initially adherent in our sample, but, by 5 months, the AI adherence of more than one-third of the sample dropped below the 80% cut point for suboptimal adherence.(Murphy et al., 2012) The MPR trajectories also showed adherence dropping below 80% early in the prescribed treatment (Winn et al., 2019). We found average adherence rates lower than Zhao et al. (2021), who found an adherence rate of 82.8% to endocrine therapy in the first year, utilizing MPRs from claims data in a large sample (Zhao et al., 2021). Possession of a medication as assessed via MPR, does not equate to taking the medication, nor are daily patterns of administration tracked as they are using (Dunbar-Jacob et al., 2010). Although there is no gold standard for measuring adherence, the MEMS® cap is superior to MPR as the MEMS® cap captures daily at-home medication-taking events (Lam, 2015).

Not using a thyroid replacement at baseline and not using an antidepressant at baseline were factors for high/slow decrease group membership and persistently high group membership (trend), respectively. These factors for adherence may be a proxy for the comorbid conditions they treat. For example, symptoms associated with low thyroid hormone levels mimic arthralgias which are often also attributed to aromatase inhibitor effects (Tagoe et al., 2019). Reviews summarized reports that hypothyroidism is associated with NSB such as cognitive problems and depression (Davis & Tremont, 2007), as well as fatigue (Kaltsas et al., 2010) and anxiety (Pelúcio et al., 2016). Future research should include hypothyroidism as a factor. Baseline antidepressant use may suggest comorbid neuropsychological symptoms, which often manifest as physical symptoms, affecting health and behaviors. Additionally, it may be that women who already take medications regularly have better more confidence (self-efficacy) in taking the new prescription of anastrozole. Higher self-efficacy is associated with better adherence (Kimmick et al., 2015; Wouters et al.,

2014). It may also be that women who are accustomed to taking medications are more likely to have established strategies (Wagner & Ryan, 2004) for successfully taking medications as prescribed but a systematic review suggested an increased regimen complexity decreased adherence (Alves-Conceicao et al., 2018).

Identifying timing for interventions is important, and these results suggest *very early intervention and monitoring* from pre-initiation to five months post-initiation may benefit adherence. However, we acknowledge that suboptimal adherence is a complex problem, and effective adherence interventions are needed (Nieuwlaat et al., 2014; Rosenberg et al., 2020). For endocrine therapy, pre-therapy symptoms have been associated with suboptimal adherence (Kidwell et al., 2014). It may be helpful to assess and manage neuropsychological symptom burden at pretherapy to mitigate the potential negative influence of these symptoms on AI adherence, but efficacious interventions will need to be developed and tested (Chan et al., 2020). Yussof et al. (2022) identified multilevel factors for endocrine therapy adherence, but modifiable factors may need further study (Yussof et al., 2022). Our results indicate that timing for an intervention should occur when prescribed, to mitigate the drop we have seen in the first 5 months. Clinicians should regularly and nonjudgmentally assess for adherence and barriers women may experience.

4.7.2 Neuropsychological Symptom Burden (NSB) Trajectories and Risk Factors

Neuropsychological symptom burden (NSB) trajectories were also conducted for use in dual trajectory modeling. Limited by the small trajectory group sizes, we chose a 3-group model for NSB trajectories, which did not appreciably change from pre-anastrozole through 18-months—low/stable, moderate/stable, and moderate-/increasing. In a previous analysis of the larger sample of 360 postmenopausal women with HR+BC, we found five trajectories of neuropsychological

symptom burden from pre-anastrozole through 18 months of therapy—three trajectories were *unchanged over time* suggesting that pre-AI symptoms did not substantially change after AI initiation, and two trajectories increased slightly, indicating a small increase in neuropsychological symptom burden. This study sample consisted of 291 of the 360 women, who also had adherence data for the dual trajectory modeling, and the 3-group NSB trajectory results were similar—two NSB trajectories were unchanged over time and one NSB trajectory increased slightly.

Risk factors varied by groups. Slightly younger age was a factor for group membership in the two higher NSB trajectories. Others have found younger age as a factor greater NSB (Rosenberg et al., 2015). Baseline antidepressant use was a risk factor for moderate/stable and moderate/increasing groups. It makes sense if women who had depressive symptoms were treated for them. However, we are not certain that the antidepressants were prescribed to treat NSB, as these medications have utility for problems with sleep and pain (Everitt et al., 2018; Sansone & Sansone, 2008). Also, it is notable that these women were *still experiencing some increased level of NSB.* We did not measure adherence to antidepressants; improving adherence or adjusting dosage may improve NSB or additional modalities that may be used to improve NSB in these women. Non-use of calcium & vitamin D was a risk factor for the moderate/increasing group membership. A relationship with vitamin D and NSB, particularly for cognitive function, may help to explain this finding (Di Somma et al., 2017). Baseline narcotic analgesic use risk factors for the moderate/stable and moderate/increasing group membership could suggest co-occurring pain, but may also be related to NSB, especially cognitive function (Cherrier et al., 2009). Notably, prescribing practices have changed since the opioid crisis began.

4.7.3 Dual Trajectories and Risk Factors

Finally, we explored dual trajectories for anastrozole adherence and NSB. Dual trajectories for adherence given symptom burden suggested that women in the low/stable NSB group had a greater probability of membership in the persistently high adherence group through 18-months post-initiation of anastrozole. While this does not confirm that symptom burden *is reduced* with adherence as Kyvernitakis et al. reported, it does suggest that, for most women, being adherent to anastrozole is *not associated with* increased symptoms in the first 18 months post-initiation (Kyvernitakis et al., 2014). However, probabilities of being in the high/slow decrease adherence group increased as NSB increased, the probabilities were still fairly low. Evaluation of this effect in a larger sample or in a subset of women for whom symptoms affect their adherence is warranted. When reversing the dual trajectories to NSB given adherence, results were similar suggesting that there may be bi-directional relationship (NSB affects adherence, adherence affects NSB) for certain groups.

4.7.4 Limitations

There are some limitations to this study. These data were from a study that was not examining adherence as a primary endpoint. It is possible that the sample was biased toward adherence by asking women to identify periods of MEMS® cap non-use. Additionally, our sample may be biased toward adherence because women who did not fill their initial AI prescription were not eligible. Studies have found that one-quarter to one-third of women do not fill their initial endocrine therapy prescription (Bowles et al., 2012; Camacho et al., 2017). The symptoms used in the model were neuropsychological. Though we found significant moderate to strong correlations

among many symptom types over time, trajectories for other symptoms may yield different results. Future research should address this gap. We referred to the category of baseline medication regimen as medication "use", however, we want to emphasize that this is self-report and acknowledge that we cannot know for certain that women were adhering to their baseline medication regimen. We did not have an economic variable in this sample, and future studies should include one. Our study sample was predominantly White, and results may not be generalizable to a diverse population.

4.7.5 Conclusion

Anti-cancer therapy adherence is a complex, multifactorial phenomenon suggested by leading adherence researchers decades ago (Gritz et al., 1989). This study furthers efforts to understand the complex relationship between AI adherence and NSB by identifying timing for potential interventions and phenotypic risk factors to identify women at risk for suboptimal adherence trajectories. Future work should address potential biological, genotypic underpinnings of NSB and adherence.

Appendix A Data-Based Manuscript (section 3.0) Tables and Figures and Supplementary Materials

Appendix Table 1 Participant Characteristics at Pre-anastrozole (N=360)

Characteristic	Mean±SD or N (%)	Symptom Trajectory Group				
		low-stable	low-increasing	moderate-stable	high-stable	high-increasing
Age in years	61.0±6.3	62.0±6.8	61.7±6.1	59.7±5.7	59.1±6.0	58.1±5.2
*** Range**	40-75	40-75	44-75	45-75	47-69	49-67
Education in years	14.8±2.7	15.0±2.9	14.9±2.7	14.9±2.5	14.3±2.6	13.5±2.0
Range	8-23	9-23	12-22	11-21	8-19	12-18
Race, White	349 (96.9)	115 (95.8)	118 (99.2)	73 (97.3)	30 (96.8)	13 (86.7)
Marital status Married/living with partner	249 (69.2)	81 (67.5)	86 (72.3)	57 (76.0)	17 (54.8)	8 (53.3)
Cancer, Stage I	241 (66.9)	84 (72.4)	80 (67.2)	52 (71.2)	14 (48.3)	11 (78.6)
Received chemotherapy, yes	110 (30.6)	30 (25.0)	34 (28.6)	29 (38.7)	13 (41.9)	4 (26.7)
Received radiation therapy, yes	251 (69.7)	89 (94.7)	85 (92.4)	48 (88.9)	21 (100)	8 (80.0)
Initial surgery Breast conserving & biopsy	243 (67.5)	71 (65.1)	85 (73.9)	54 (75.0)	22 (81.5)	11 (78.6)
Number of medications reported at baseline	6.0±3.6	5.6±3.4	5.9±3.5	6.3±3.5	7.0±4.2	7.0±3.8
Range	0-16	0-16	0-16	0-16	1-16	3-16
Baseline Medication Categories (pre-anastrozole time point)						
Non-narcotic analgesics*	132 (36.7)	34 (28.3)	41 (34.5)	40 (53.3)	11 (35.5)	6 (40.0)
Narcotic analgesics*	30 (8.3)	6 (5.0)	6 (5.0)	8 (10.7)	5 (16.1)	5 (33.3)
Calcium/vitamin D*	185 (51.4)	71 (59.2)	64 (53.8)	36 (48.0)	11 (35.5)	3 (20.0)
Antidepressants*	76 (21.2)	8 (6.7)	18 (15.1)	28 (37.3)	12 (38.7)	10 (66.7)
Thyroid	67 (18.6)	21 (17.5)	24 (20.2)	12 (16.0)	6 (19.4)	4 (26.7)
Gastrointestinal reflux	75 (20.8)	25 (20.8)	22 (18.5)	14 (18.7)	9 (29.0)	5 (33.3)
Vitamin/mineral	230 (63.9)	76 (63.3)	77 (64.7)	49 (65.3)	19 (61.3)	9 (60.0)
Herbal supplement	115 (31.9)	37 (30.8)	39 (32.8)	29 (38.7)	5 (16.1)	5 (33.3)
Anti-cholesterol	104 (28.9)	41 (34.2)	34 (28.6)	16 (21.3)	8 (25.8)	5 (33.3)
Anti-anxiety*	34 (9.4)	5 (4.2)	9 (7.6)	11 (14.7)	8 (25.8)	1 (6.7)
Diabetes/insulin	39 (10.8)	12 (10.0)	12 (10.1)	7 (9.3)	4 (12.9)	4 (26.7)

Appendix Table 2 Pearson Correlation Coefficients at Pre-anastrozole, 6-, 12-, and 18-months for Self-reported Neuropsychological Symptoms (depression, anxiety, fatigue, and cognitive symptoms).

Scale	Time (Months)	BCPT-cog	POMS F/I	POMS T/A
BDI-II	Pre-anastrozole	.48	.57	.54
	6	.54	.63	.57
	12	.60	.68	.64
	18	.67	.71	.68
BCPT-cog	Pre-anastrozole	1	.47	.45
	6		.43	.55
	12		.45	.60
	18		.58	.54
POMS F/I	Pre-anastrozole		1	.57
	6			.53
	12			.68
	18			.75

Note: BDI-II=Beck Depression Inventory-II; POMS T/A=Profile of Mood States Tension/Anxiety Subscale; POMS F/I=Profile of Mood States Fatigue/Inertia Subscale; BCPT-cog= Breast Cancer Prevention Trial Checklist cognitive subscale.
All results were p<.001.

Appendix Table 3 Exploratory Factor Analysis with Varimax Rotation, Forced 5-factor Model from Pre-anastrozole, 6-, 12-, and 18-months Post-initiation

Rotated Component Matrix						
Measure	Time (Months)	Dimension				
		1 NSB	2 GI	3 Bladder/Gyne	4 Dyspareunia	5 Weight
BCPT Cognitive Subscale	Pre-anastrozole	**.61**	.26	.31	.22	
	6	**.73**		.24		
	12	**.74**			.28	
	18	**.76**	.38			
BDI-II Total Score	Pre-anastrozole	**.79**				
	6	**.79**				
	12	**.86**				
	18	**.82**				
POMS T/A Tension-Anxiety Subscale	Pre-anastrozole	**.85**				
	6	**.87**				
	12	**.85**				
	18	**.82**				
POMS F/I Fatigue-Inertia Subscale	Pre-anastrozole	**.80**				
	6	**.74**	.37			
	12	**.81**	.24	.25		
	18	**.86**				
BCPT Dyspareunia Subscale	Pre-anastrozole			**.73**	.43	
	6				**.89**	
	12				**.88**	
	18	.21	**.76**	.48		
BCPT Gynecological Subscale*	Pre-anastrozole	.23		**.76**		
	6		.34	**.57**	.40	.23
	12		**.71**		.37	.24
	18	**.62**			.51	
BCPT Gastrointestinal Subscale*	Pre-anastrozole		**.79**			
	6	.21	**.74**			
	12		**.84**			
	18	.46		.46		
BCPT Weight Concerns Subscale*	Pre-anastrozole		**.80**	.25		
	6					**.95**
	12					**.87**
	18	**.51**		.21		
BCPT Bladder Control Subscale	Pre-anastrozole					**.95**
	6	.26		**.88**		
	12	.21		**.82**	.26	.25
	18	.52			**.59**	
BCPT Vasomotor Subscale	Pre-anastrozole	.26			**.86**	
	6		**.75**		.23	
	12	.21	.27	**.67**		
	18	.51		.32		**.60**

*Extraction method was Principal Component Analysis; rotation method was Varimax with Kaiser Normalization. *Subscales were determined using Terhorst et al. 2011. NSB=neuropsychological symptom burden. BDI-II=Beck Depression Inventory-II; POMS =Profile of Mood States; BCPT-cog= Breast Cancer Prevention Trial Checklist. Bolded numbers indicate measure correlation is highest for that dimension. Did not display factor loadings < .20. Loading cut point was >.60, and consistent loadings over time were necessary. Pre-anastrozole, 6-, 12-, and 18-month time points Kaiser-Meyer-Olkin Measure of Sampling Adequacy were .829, .810, .783, and .827, respectively. Bartlett's Test of Sphericity results were significant p<.001 at all time points.*

Appendix Table 4 Neuropsychological Symptom Burden (NSB) Trajectory Results

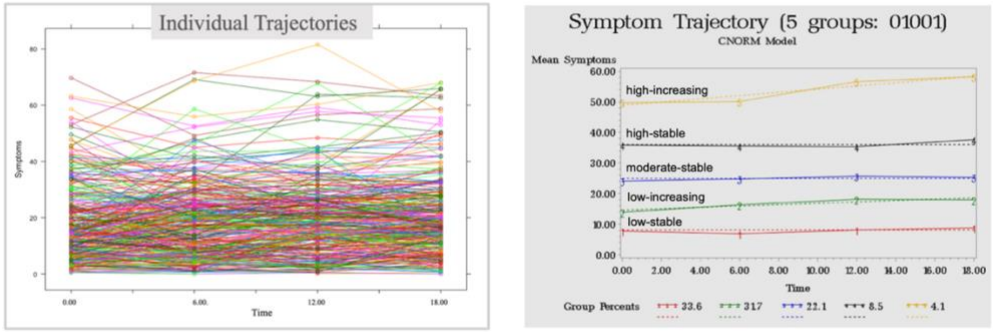
Symptom Trajectory 1-group Model BIC1= - 5713.20 (N= 360) BIC2= -5715.28 (N= 1440) AIC= -5707.37							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
1	1	b_0=17.40 b_1=0.14	1.00	N/A	1.00	1.00	N/A
Symptom Trajectory 2-group Model BIC1= -5383.03 (N= 360) BIC2= -5386.50 (N= 1440) AIC= -5373.32							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
10	1	b_0=13.40 b_1=0.14	.827	.788, .866	.833	.982	11.738
	2	b_0= 38.38	.173	.134, .212	.167	.949	89.454
Symptom Trajectory 3-group Model BIC1= -5199.78 (N= 360) BIC2= -5206.02 (N= 1440) AIC= -5182.30							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
111	1	b_0=9.29 b_1=0.13	.537	.485, .589	.539	.955	18.235
	2	b_0=23.45 b_1=0.11	.386	.336, .436	.383	.938	24.244
	3	b_0=43.56 b_1=0.39	.077	.049, .105	.078	.977	499.411
Symptom Trajectory 4-group Model BIC1= -5122.42 (N= 360) BIC2= -5130.74 (N= 1440) AIC= -5099.11							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
1101	1	b_0=8.13 b_1=0.12	.445	.394, .496	.433	.961	29.381
	2	b_0=19.76 b_1=0.15	.398	.347, .449	.411	.910	15.350
	3	b_0=34.29	.116	.083, .149	.114	.934	108.640
	4	b_0=48.79 b_1=0.53	.042	.021, .063	.042	.998	10,929.968
Symptom Trajectory 5-group Model BIC1= -5104.24 (N= 360) BIC2= -5112.56 (N=1440) AIC= -5080.93							
Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
01001	1 low-stable	b_0=7.85	.336	.287, .385	.333	.918	22.266
	2 low-increasing	b_0=14.50 b_1=0.23	.317	.269, .365	.331	.817	9.614
	3 moderate-stable	b_0=24.97	.221	.178, .264	.208	.880	25.748
	4 high-stable	b_0=36.09	.085	.056, .114	.086	.914	115.035
	5 high-increasing	b_0=48.88 b_1=0.53	.041	.021, .061	.042	.992	2,835.610

Note: BIC= Bayesian information criterion, BIC1 (sample), BIC2 (observations); AIC= Akaike information criterion; trajectory polynomial orders in parameter column b_0=intercept, b_1=linear; estimated and assigned group membership should be similar with a narrow CI for estimated group membership; AvePP= average posterior probability (>.70 is preferred); OCC= odds of correct classification (>5 is preferred).

Appendix Table 5 Comparison of Multinomial Logistic Regression Predictors to Bootstrapping Confidence Intervals by Group (N=360)

			Multinomial Logistic Regression: odds ratio (confidence intervals) Bootstrapping: (confidence intervals)			
Group Predictors	Low-stable 1 (reference)		Low-increasing 2	Moderate-stable 3	High-stable 4	High-increasing 5
Age	1	Regression	0.99 (0.96, 1.04)	**0.95 (0.90, 0.99)**	**0.93 (0.87, 0.99)**	**0.90 (0.81, 0.99)**
		Bootstrapping	(-0.05, 0.04)	(-0.11, 0.00)	(-0.15, 0.00)	(-0.20, -0.04)
Antidepressants	1	Regression	2.39 (0.99, 5.77)	**7.57 (3.15, 18.22)**	**7.48 (2.62, 21.31)**	**29.40 (7.36, 117.52)**
		Bootstrapping	(-0.35, 2.72)	(0.78, 4.36)	(0.55, 3.83)	(1.34, 23.89)
Calcium/vitamin D	1	Regression	0.83 (0.49, 1.40)	0.74 (0.39, 1.41)	0.50 (0.21, 1.20)	**0.14 (0.30, 0.61)**
		Bootstrapping	(-0.70, 0.31)	(-0.94, 0.28)	(-1.71. 0.19)	(-15.84, -0.89)
Non-narcotic analgesics	1	Regression	1.34 (0.77, 2.34)	**2.99 (1.57, 5.68)**	1.40 (0.58, 3.41)	1.73 (0.50, 5.92)
		Bootstrapping	(-0.26, 0.91)	(0.40, 1.83)	(-.070, 1.20)	(-1.06, 1.80)
Narcotic analgesics	1	Regression	0.94 (0.29, 3.04)	1.94 (0.58, 6.43)	3.14 (0.80, 12.29)	**12.12 (2.51, 58.52)**
		Bootstrapping	(-1.31, 1.18)	(-0.69, 2.06)	(-0.32, 2.42)	(0.27, 5.56)
Anti-anxiety	1	Regression	1.68 (0.54, 5.26)	2.91 (0.89, 9.48)	**5.16 (1.43, 18.66)**	0.74 (0.72, 7.63)
		Bootstrapping	(-0.60, 1.87)	(-0.17, 3.03)	(0.18, 3.58)	(-19.95, 1.28)

Note: Pseudo R-square Cox and Snell= 0.26; Nagelkerke=0.27; McFadden=0.11. Model Chi-square 106.34 (df=24) p<.01. Bolded regression values are significant.



Appendix Figure 1 Neuropsychological Symptom Burden (NSB) Trajectories Pre-anastrozole through 18-months Post-initiation for Individual[a] and 5-group Model for 360 Women

Note: Time points: pre anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; CNORM= censored normal; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 01001= intercept, linear, intercept, intercept, linear.

[a]Individual trajectories were graphed using RStudio Version 1.4.1106 © 2009-2021 RStudio, PBC "Tiger Daylily" (2389bc24, 2021-02-11) for macOS

Appendix A.1 Appendix Sub-section Data-Based Manuscript (section 3.0)

Supplementary Materials

Appendix Supplementary Table 1 Description of Self-reported Symptom Measures Used for Correlational Analyses

Measure	Description	Concepts Measured
Breast Cancer Prevention Trial (BCPT) checklist [1-4]	42-item survey of the previous 4 weeks Total score and 8 subscales 5-point Likert scale symptom absent: 0 'not at all'; or symptom present: 1 'slightly'; 2 'moderately'; 3 'quite a bit'; and 4 'extremely'	Self-reported physical and psychological symptoms
Brief Pain Inventory (BPI) [5]	11-item survey 0-10 scale with higher scores indicating more pain or interference	Pain level pain interference w/activity
Profile of Mood States (POMS) [6, 7]	anxiety subscale and fatigue subscale to describe feelings or mood using a Likert '0= not at all' to '4=extremely'	Anxiety and fatigue
Beck Depression Inventory-II (BDI) [8-10]	21-item measure of depressive symptoms, often used clinically	Depressive symptoms
Pittsburgh Sleep Quality Index (PSQI) [11]	Sleep times, hours, and Likert scaled questions assess sleep quality for past month	Sleep
Epworth Sleepiness Scale [12]	8-item 4-point Likert 0 = 'Would never doze' to 3 = 'High chance of dozing'	Daytime sleepiness
Psychological Sense of Economic Hardship [13]	20-item patient report of financial distress with Likert response subscales of financial strain, inability to make ends meet, and not enough money for necessities, followed by several yes/no item responses	Financial strain

Appendix A.1.1 Notes on Sample Size for Trajectory Analysis

There is no power calculation for group-based trajectory modeling. Loughran & Nagin (2006) found that a sample as low as 500 can estimate a "true population value" [14], but also noted that some researchers have used a smaller sample size appropriately. It is worth noting that researchers have used trajectory analysis in samples as low as 126 [15] and 130 [16]. For example, Park et al (2020) [15], reported a 2-group trajectory analysis in the sample of 126.

The sample in combination with the variable of interest limits the ability to conduct the analysis as shown by the fit and diagnostics of the models. The appropriateness of the sample size (and variability) is reflected in the ability to conduct the trajectory modeling in the fit and diagnostics table. We were transparent by providing each best fitting model results as groups were added to the models.

We should note that results do not imply that every sample tested will have the same number and shape of trajectories. Thus, these results should be evaluated in another sample to see if they can be replicated. We chose the 5-group model based on the detail provided among the groups, the diagnostics, and fit, noting that women who are in the high groups experience greater NSB, and therefore, are important clinically.

Appendix Supplementary Table 2 Strength of Correlations Among Symptom Measures

Measure	PSQI1	PSQI2	PSQI3	PSQI4	PSQI5	PSQI6	PSQI7	EH FS	EH IMEM	EH NEMN	EH EAC	BDI-II	POM T/A	POM F/I	BPI sev.	BPI int	Epworth
EH FS	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 ns	1 - 2 - 3 S 4 ns	1 - 2 - 3 ns 4 M										
EH IMEM	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 S 4 ns	1 - 2 - 3 ns 4 M										
EH NEMN	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 ns										
EH EAC	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 - 2 - 3 - 4 ns	1 - 2 - 3 ns 4 M	1 - 2 - 3 ns 4 ns										
BDI-II	**1 S** **2 M** **3 M** **4 M**	1 W 2 M 3 W 4 M	1 ns 2 W 3 ns 4 ns	1 W 2 W 3 ns 4 ns	1 M 2 W 3 M 4 S	1 W 2 ns 3 ns 4 ns	**1 S** **2 S** **3 S** **4 S**	1 ns 2 ns 3 M 4 ns	**1 M** **2 M** **3 M** **4 S**	1 ns 2 M 3 M 4 M	1 ns 2 W 3 S 4 ns						
POM T/A	1 S 2 M 3 ns 4 M	1 M 2 M 3 ns 4 M	1 ns 2 ns 3 ns 4 ns	1 W 2 ns 3 ns 4 ns	1 M 2 ns 3 M 4 S	1 ns 2 ns 3 ns 4 ns	**1 M** **2 S** **3 M** **4 M**	1 ns 2 W 3 S 4 ns	**1 M** **2 M** **3 M** **4 M**	1 ns 2 M 3 M 4 ns	1 ns 2 ns 3 ns 4 ns	**1 S** **2 S** **3 S** **4 S**					
POM F/I	1 M 2 M 3 W 4 M	1 M 2 M 3 W 4 M	1 ns 2 W 3 ns 4 ns	1 W 2 W 3 ns 4 ns	1 M 2 W 3 W 4 S	1 ns 2 ns 3 ns 4 ns	**1 M** **2 S** **3 M** **4 S**	1 ns 2 ns 3 M 4 M	1 ns 2 M 3 M 4 S	1 ns 2 ns 3 S 4 M	1 ns 2 ns 3 M 4 ns	**1 S** **2 S** **3 S** **4 S**	**1 S** **2 S** **3 S** **4 S**				
BPI sev.	1 ns 2 ns 3 ns 4 W	1 ns 2 W 3 ns 4 W	1 ns 2 W 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 M 2 ns 3 W 4 M	1 ns 2 ns 3 ns 4 W	1 ns 2 M 3 ns 4 M	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 S 4 S	1 ns 2 ns 3 M 4 S	1 ns 2 ns 3 M 4 ns	1 W 2 M 3 M 4 M	1 W 2 W 3 M 4 M	1 W 2 M 3 M 4 M			
BPI int	1 ns 2 M 3 ns 4 M	1 ns 2 M 3 M 4 M	1 ns 2 W 3 ns 4 ns	1 ns 2 M 3 ns 4 ns	**1 M** **2 M** **3 M** **4 S**	1 W 2 W 3 M 4 W	1 W 2 S 3 W 4 S	1 ns 2 ns 3 M 4 M	**1 M** **2 M** **3 S** **4 M**	1 ns 2 ns 3 S 4 M	1 ns 2 ns 3 ns 4 ns	**1 M** **2 S** **3 S** **4 S**	1 W 2 M 3 M 4 S	**1 M** **2 S** **3 S** **4 S**			
Epworth	1 ns 2 ns 3 ns 4 M	1 ns 2 W 3 ns 4 ns	1 W 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 M 3 M 4 M	1 ns 2 W 3 W 4 ns	1 M 2 W 3 ns 4 S	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 S	1 - 2 - 3 ns 4 ns	1 - 2 - 3 ns 4 ns	1 ns 2 W 3 M 4 M	1 ns 2 ns 3 M 4 ns	1 M 2 ns 3 W 4 M	1 W 2 ns 3 M 4 M	1 W 2 ns 3 W 4 M	
BCPT cog	1 W 2 M 3 W 4 ns	1 M 2 W 3 ns 4 W	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 W 3 W 4 M	1 ns 2 W 3 W 4 W	**1 M** **2 S** **3 M** **4 S**	1 ns 2 ns 3 M 4 ns	1 ns 2 M 3 ns 4 S	1 ns 2 ns 3 ns 4 S	1 ns 2 ns 3 S 4 M	**1 M** **2 S** **3 S** **4 S**	**1 M** **2 S** **3 S** **4 S**	**1 M** **2 M** **3 M** **4 S**	1 W 2 W 3 M 4 M	**1 M** **2 M** **3 M** **4 M**	**1 M** **2 M** **3 M** **4 M**
BCPT musc	1 W 2 M 3 M 4 W	1 W 2 W 3 M 4 M	1 ns 2 W 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 M 2 W 3 M 4 S	1 ns 2 W 3 W 4 W	1 W 2 M 3 M 4 S	1 ns 2 ns 3 S 4 ns	1 ns 2 M 3 M 4 S	1 ns 2 ns 3 M 4 S	1 ns 2 ns 3 M 4 M	**1 M** **2 M** **3 S** **4 S**	**1 M** **2 M** **3 S** **4 S**	**1 S** **2 M** **3 S** **4 S**	**1 S** **2 S** **3 S** **4 S**	**1 S** **2 S** **3 S** **4 S**	**1 M** **2 M** **3 M** **4 S**
BCPT vaso	1 ns 2 M 3 ns 4 ns	1 ns 2 ns 3 ns 4 W	1 ns 2 ns 3 ns 4 ns	1 ns 2 W 3 ns 4 ns	1 ns 2 M 3 W 4 M	1 M 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 M 3 W 4 M	1 W 2 W 3 W 4 W	1 W 2 M 3 M 4 M	1 W 2 ns 3 W 4 W	1 W 2 W 3 M 4 M	1 ns 2 ns 3 ns 4 ns
BCPT GI*	1 ns 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 W	1 ns 2 ns 3 ns 4 ns	1 ns 2 W 3 ns 4 ns	1 W 2 M 3 M 4 S	1 ns 2 ns 3 M 4 ns	1 ns 2 M 3 W 4 ns	1 ns 2 ns 3 S 4 ns	1 ns 2 W 3 W 4 W	1 ns 2 ns 3 S 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 W 3 W 4 W	1 W 2 W 3 W 4 W	1 M 2 M 3 M 4 M	1 W 2 W 3 W 4 W	1 M 2 W 3 W 4 W	1 ns 2 W 3 ns 4 W
BCPT dys	1 M 2 W 3 M 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 ns 3 ns 4 W	1 ns 2 ns 3 ns 4 ns	1 M 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 W 3 W 4 ns	1 ns 2 W 3 W 4 ns	1 W 2 ns 3 ns 4 ns	1 W 2 W 3 ns 4 ns	1 W 2 W 3 W 4 W	1 W 2 ns 3 ns 4 ns
BCPT BC	1 ns 2 W 3 ns 4 ns	1 ns 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 M	1 W 2 W 3 ns 4 M	1 W 2 M 3 M 4 M	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 M 4 M	1 ns 2 ns 3 M 4 M	1 W 2 M 3 M 4 M	1 W 2 W 3 M 4 M	1 W 2 M 3 M 4 M	1 W 2 M 3 M 4 M	1 W 2 M 3 M 4 M	1 ns 2 ns 3 ns 4 ns
BCPT WC*	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 ns 3 W 4 S	1 ns 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 W	1 ns 2 ns 3 S 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 W 2 W 3 W 4 M	1 W 2 W 3 W 4 M	1 W 2 W 3 W 4 M	1 W 2 ns 3 ns 4 W	1 W 2 W 3 ns 4 M	1 ns 2 ns 3 W 4 M
BCPT gyne*	1 ns 2 ns 3 W 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 ns	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 ns 4 W	1 ns 2 M 3 M 4 S	1 ns 2 ns 3 S 4 ns	1 M 2 M 3 ns 4 S	1 ns 2 ns 3 ns 4 M	1 ns 2 ns 3 ns 4 ns	1 W 2 W 3 W 4 M	1 W 2 W 3 W 4 M	1 W 2 W 3 W 4 M	1 W 2 W 3 ns 4 M	1 W 2 W 3 ns 4 M	1 ns 2 ns 3 ns 4 M

Note: correlation results W=Weak r ≤ 0.299; M=Moderate r between 0.3 - 0.499; S=Strong r≥ 0.5; ns=not significant; - = not variable cannot be calculated. Bolded, green-filled cells were to show cells with consistent moderate-strong correlations. PSQI= Pittsburgh Sleep Quality Index PSQI subscales are PSQI 1=sleep quality, PSQI 2=sleep latency, PSQI 3=sleep duration, PSQI 4=habitual sleep efficiency, PSQI 5=sleep disturbance, PSQI 6=use of sleep meds, and PSQI 7=daytime dysfunction; BDI-II=Beck Depression Inventory-II; EH= Psychological Sense of Economic Hardship EH subscales are FS=financial strain, IMEM=inability to make ends meet, NEMN=not enough money for necessities, and EAC=economic adjustments and cutbacks; POMS T/A=Profile of Mood States Tension/Anxiety Subscale; POMS F/I=Profile of Mood States Fatigue/Inertia Subscale; Epworth=Epworth Sleepiness Scale; BCPT= Breast Cancer Prevention Trial BCPT subscales are cog=cognitive, musc= musculoskeletal, vaso=vasomotor, GI=gastrointestinal, dys=dyspareunia, BC=bladder control, WC*=weight concerns, and gyne*=gynecological. *Subscales were determined using Terhorst et al. 2011.*

Appendix Supplementary Table 3 Descriptive Statistics for the Four Individual Symptom Measures and the Derived Neuropsychological Symptom Burden (NSB) Composite at Pre-anastrozole, 6-, 12-, and 18-months

Measure (Possible Range)	Mean ± Standard Deviation			
	Pre-anastrozole	6-months	12-months	18-months
Beck Depression Inventory II, total score (0-63)	5.96±5.61	6.15±5.72	7.20±6.23	6.78±5.71
Profile of Mood States, anxiety subscale (0-36)	6.70±5.08	6.82±5.13	6.90±4.89	7.40±4.97
Profile of Mood States, fatigue subscale (0-28)	6.67±6.35	6.55±5.37	7.08±5.13	7.05±5.05
BCPT Checklist, cognitive subscale (0-12)	2.15±2.19	2.41±2.20	2.64±2.17	2.74±2.23
Neuropsychological Symptom Burden (NSB) (0-100)	17.44±12.87	18.04±12.67	19.48±12.84	19.83±13.00

Appendix Supplementary Table 4 Patient and Clinical Characteristics comparisons with Trajectory Group Membership to Screen for Use in Regression

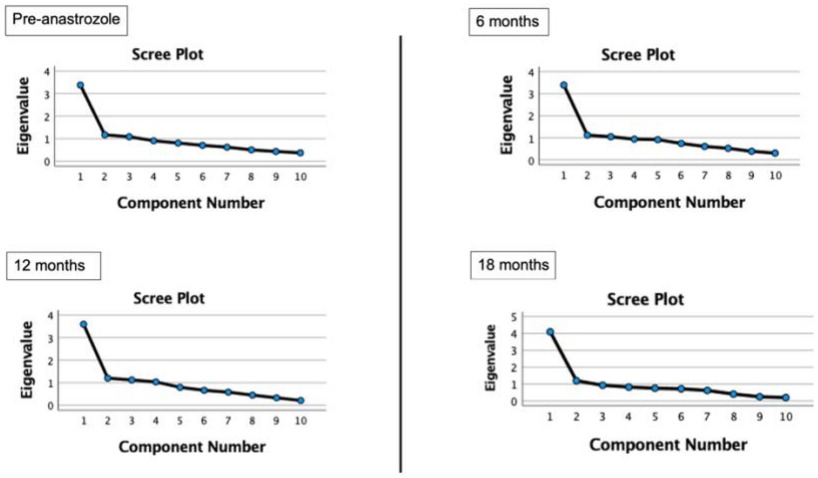
Characteristic	*F* statistic	*p*-value
Age*	3.57	<.01
Education in years	1.47	.21
Number of medications at baseline	1.42	.22
Characteristic	**Pearson chi-square**	***p*-value**
Race, White	7.86	.09 FE
Married/living with partner, yes	7.08	.13 FE
Stage I BC, yes	7.34	.12FE
Chemotherapy, yes	6.29	.18FE
Received radiation therapy, yes	5.38	.20 FE
Initial surgery breast conserving & biopsy, yes	25.98	.17
Medication categories at baseline, yes		
Thyroid medications	1.28	.87FE
Gastrointestinal reflux medications	3.30	.51FE
Vitamin/mineral supplements	0.31	.99
Herbal supplements	5.24	.26FE
Anti-cholesterol medications	4.00	.41FE
Diabetes/insulin medications	4.36	.36 FE
Anti-depressants*	53.90	<.01FE
Non-narcotic analgesic*	12.90	.01
Narcotic analgesics*	18.71	<.01FE
Anti-anxiety*	16.63	<.01FE
Calcium/vitamin D supplements*	12.58	.014

**= statistical significance p<.05; Kruskal Wallis used for continuous variables, Chi-square for categorical; FE=Fisher's Exact; degrees of freedom=4*

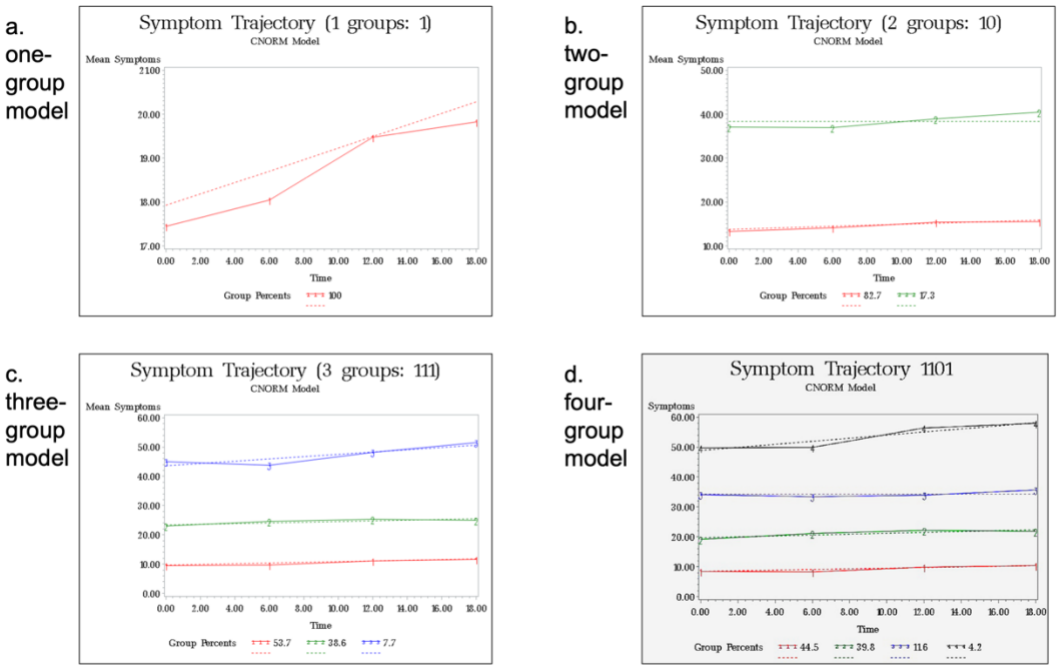
Appendix Supplementary Table 5 Regression of Risk Factors for NSB Trajectory Group Membership Using PROC TRAJ

NSB with Phenotypic Risk Factors BIC1= -5119.90 (N= 360) BIC2= -5144.85 (N= 1440) AIC= -5013.95				
Group	Parameter	Estimate	Standard Error	p-value
low-stable	Baseline (reference)	(0)		
low-increasing	Constant	0.647	1.630	.691
	Age	-0.012	0.026	.641
	Antidepressant use	0.998	0.568	.080
	Calcium/Vitamin D use	-0.253	0.318	.426
	Non-narcotic analgesic use	0.282	0.347	.416
	Narcotic use	-0.149	0.733	.839
	Anti-anxiety use	0.134	0.743	.857
moderate-stable	Constant	3.139	1.906	.100
	Age	**-0.077**	**0.032**	**.016**
	Antidepressant use	**2.399**	**0.531**	**<.001**
	Calcium/Vitamin D use	-0.272	0.382	.477
	Non-narcotic analgesic use	**1.243**	**0.390**	**.002**
	Narcotic use	0.553	0.700	.430
	***Anti-anxiety use**	**1.345**	**0.648**	**.038**
high-stable	Constant	3.000	2.337	.199
	Age	**-0.082**	**0.039**	**.035**
	Antidepressant use	**2.251**	**0.611**	**<.001**
	Calcium/Vitamin D use	-0.766	0.490	.119
	Non-narcotic analgesic use	0.491	0.493	.319
	Narcotic use	1.178	0.747	.115
	Anti-anxiety use	**1.650**	**0.697**	**.018**
high-increasing	Constant	4.084	3.145	.194
	Age	**-0.121**	**0.054**	**.025**
	Antidepressant use	**3.619**	**0.763**	**<.001**
	Calcium/Vitamin D use	**-2.013**	**0.783**	**.010**
	Non-narcotic analgesic use	0.632	0.657	.336
	Narcotic use	**2.401**	**0.842**	**.004**
	Anti-anxiety use	-0.356	1.340	.791

*Note: * variable was an additional finding to the multinomial logistic regression. Bolded text indicates p<.05.*



Appendix Supplementary Figure 1 Scree Plots for Factor Analyses Over Time



Appendix Supplementary Figure 2 Trajectory Models for a) One-, b) Two-, c) Three-, and d) Four-Groups

Note: Time points: pre anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; CNORM= censored normal; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 10= linear, intercept.

Appendix A.1.2 Supplementary References

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Appendix B Tables and Figures for Data-based Manuscript (section 4.0)

Appendix Table 6 Participant Characteristics at Pre-anastrozole (n=291) for Adherence Trajectory Groups

Baseline Characteristics	Total Sample	Adherence Trajectory Group				
		Very Low	Low	High/ Sharp Decrease	High/ Slow Decrease	Persistently High
		Mean ± SD or N (%)				
Age (years) Range (years)	60.9 ± 6.4 40-75	61.4 ± 5.1 51-74	60.8 ± 6.2 49-72	60.9 ± 4.2 53-68	60.9 ± 6.8 44-75	60.7 ± 6.6 40-74
Education (years) Range (years)	14.8 ± 2.6 9-22	14.6 ± 2.3 9-18	15.7 ± 2.3 12-18	14.5 ± 2.9 12-21	14.8 ± 2.7 10-22	14.9 ± 2.8 11-22
Race White Black More than 1 race	 282 (97) 8 (2.7) 1 (0.3)	 33 (11.7) 0 (0) 0 (0)	 23 (8.2) 1 (12.5) 0 (0)	 11 (3.9) 0 (0) 0 (0)	 130 (46.1) 5 (62.5) 0 (0)	 85 (30.1) 2 (25.0) 1 (100)
Marital status, married or living with partner	197 (67.7)	25 (12.7)	14 (7.1)	9 (4.6)	86 (43.7)	63 (32.0)
Cancer Stage Stage I Stage IIa Stage IIb Stage IIIa	 191 (65.6) 54 (18.6) 22 (7.6) 15 (5.2)	 23 (12.0) 7 (13.0) 1 (4.5) 1 (6.7)	 20 (10.5) 3 (5.6) 0 (0) 1 (6.7)	 6 (3.1) 3 (5.6) 0 (0) 2 (13.3)	 84 (44.0) 27 (50.0) 11 (50.0) 8 (53.3)	 58 (30.4) 14 (25.9) 10 (45.5) 3 (20.0)
Received chemotherapy	89 (30.6)	7 (7.9)	4 (4.5)	3 (3.4)	49 (38.3)	26 (31.0)
Received radiation therapy	215 (59.7)	28 (84.8)	18 (75.0)	8 (72.7)	96 (71.1)	65 (73.9)
Initial surgery Breast conserving & biopsy	189 (52.5)	25 (75.8)	16 (66.7)	7 (63.6)	84 (62.2)	57 (64.8)
Number of baseline medications Range	6.1 (3.5) 0-16	7.1 ± 4 4 0-16	6.4 ± 3.7 0-16	5.7 ± 3.0 1-10	5.8 ± 3.4 0-16	6.1 ± 3.4 0-16
Baseline Medication Regimen Categories						
Non-narcotic analgesics	104 (35.7)	10 (9.6)	13 (12.5)	5 (4.8)	48 (46.2)	28 (26.9)
Narcotic analgesics	29 (10.0)	4 (13.8)	3 (10.3)	1 (3.4)	16 (55.2)	5 (17.2)
Calcium/vitamin D supplements	146 (50.2)	17 (11.6)	12 (8.2)	6 (4.1)	62 (42.5)	49 (58.3)
Antidepressants*	50 (17.2)	12 (24.0)	5 (10.0)	1 (2.0)	24 (48.0)	8 (16.0)
Thyroid*	53 (18.2)	13 (24.5)	3 (5.7)	1 (1.9)	20 (37.7)	16 (30.2)
Gastrointestinal reflux	60 (20.6)	11 (18.3)	6 (10.0)	3 (5.0)	24 (40.0)	16 (26.7)
Vitamin/mineral supplements	182 (62.5)	26 (14.3)	16 (8.8)	5 (2.7)	78 (42.9)	57 (31.3)
Herbal supplements	91 (31.3)	14 (15.4)	9 (9.9)	3 (3.3)	37 (40.7)	28 (30.8)
Cholesterol	80 (27.5)	7 (8.8)	6 (7.5)	6 (7.5)	35 (43.8)	26 32.5)
Diabetes/insulin	32 (11.0)	3 (9.4)	2 (6.3)	2 (6.3)	14 (43.8)	11 (34.4)
Anti-anxiety	25 (8.6)	5 (20.0)	2 (8.0)	2 (8.0)	7 (28.0)	9 (36.0)

*Note: *p<.05 for risk factor screening.*

Appendix Table 7 Parameters and Diagnostics for Anastrozole Adherence (Panel A) and Symptom (Panel B) and Dual (Panels C & D) Trajectory Models

Panel A. Anastrozole Adherence Trajectory (n=291)
BIC1= -9887.11 (N= 291) BIC2= -9910.66 (N= 3985) AIC= -9854.05

Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
02330	1	b_0=15.577	.055	.029, .081	.055	.999	13150.338
	2	b_0=-2.408 b_1=-8.256 b_2=0.396	.062	.034, .09	.062	.998	8808.911
	3	b_0=114.195 b_1=-6.278 b_2=-0.766 b_3=0.043	.065	.037, .093	.062	.939	222.485
	4	b_0=95.385 b_1=-5.364 b_2=0.702 b_3=-0.029	.185	.14, .23	.182	.904	41.291
	5	b_0=108.724	.633	.578, .688	.643	.969	18.349

Adherence with Phenotypic Risk Factors BIC1= -9500.61 (N= 280) BIC2= -9534.61 (N=3826) AIC= -9453.36

Group	Parameter	Estimate	Standard Error	p-value
1	Baseline (reference)	(0)		
2	Constant	-0.025	0.504	.961
	thyroid use	0.045	0.713	.949
	Antidepressant use	0.350	0.730	.632
3	Constant	-0.677	0.462	.143
	Thyroid use	-1.496	0.919	.104
	Antidepressant use	-0.627	0.845	.458
4	Constant	1.659	0.402	<.001
	Thyroid use	**-1.944**	**0.801**	**.015**
	Antidepressant use	-0.391	0.664	.556
5	Constant	2.872	0.371	<.001
	Thyroid use	-.0904	0.560	.106
	Antidepressant use	**-1.089**	**0.595**	**.067**

Panel B. Symptom Trajectory (n=291)
BIC1=-4209.73 (N=291) BIC2=-4213.89 (N=11644) AIC=-4198.71

Model	Group	Estimated Parameters	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
001	1	b_0=10.121	.568	.511, .625	.570	.957	16.921
	2	b_0=24.123	.364	.309, .419	.361	.936	63.111
	3	b_0=47.193 b_1=7.461	.068	.039, .097	.069	.969	494.723

Neuropsychological Symptom Burden Trajectories with Phenotypic Risk Factors
BIC1= -4040.97 (N= 280) BIC2= -4051.36 (N=1120) AIC= -4014.71

Group	Parameter	Estimate	Standard Error	p-value
1	Baseline (reference)	(0)		
2	Constant	3.379	1.532	.028
	Antidepressant use	**1.549**	**0.405**	**<.001**
	Calcium/vitamin D use	-0.372	0.307	.226
	Narcotic analgesic use	0.823	0.497	.098
	Age	**-0.068**	**0.025**	**.007**
3	Constant	3.280	3.467	.344
	Antidepressant use	**3.088**	**0.767**	**< .001**
	Calcium/vitamin D use	**-2.994**	**1.194**	**.012**
	Narcotic analgesic use	**2.645**	**0.805**	**.001**
	Age	**-0.111**	**0.060**	**.063**

Panel C. Dual Adherence Given Symptom Trajectory (n=291)
BIC1= -14106.35 (N= 291) BIC2= -14153.76 (N= 5149) AIC= -14045.74

Group	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
1	.569	.512, .626	.570	.957	16.876
2	.363	.308, .418	.361	.933	24.451
3	.067	.038, .096	.069	.967	402.802

Panel D. Dual Symptom Given Adherence Trajectory (n=291)
BIC1= -14104.99 (N= 291) BIC2= -14152.40 (N= 5149) AIC= -14044.38

Group	Estimated Group Membership	95% CI	Assigned Group Proportion (P*)	AvePP	OCC
1	.055	.029, .081	.055	.999	25195.29
2	.062	.034, .09	.062	.999	12077.03
3	.058	.031, .085	.055	.939	249.654
4	.185	.14, .23	.182	.936	64.663
5	.641	.586, .696	.649	.962	14.211

Note: BIC= Bayesian Information Criterion; AIC= Aikake Information Criterion; AvePP= average posterior probability; OCC= odds of correct classification; trajectory parameters b_0=intercept; b_1=linear; b_2=quadratic; b_3=cubic.

Appendix Table 8 Dual Trajectory Results: Anastrozole Adherence Given Neuropsychological Symptom Burden (NSB) in 291 Women

Panel A. Dual Trajectory Adherence Given Neuropsychological Symptom Burden (NSB)

A.1. Probability of adherence group conditional on NSB group
impact of NSB on adherence

	NSB Trajectory Group		
Adherence Trajectory Group	Low/stable	Moderate/stable	Moderate/increasing
Very low	.029	.088	.103
Low	.051	.071	.102
High/sharp decrease	.057	.069	0
High/slow decrease	.127	.254	.371
Persistently high	**.736**	.518	.424

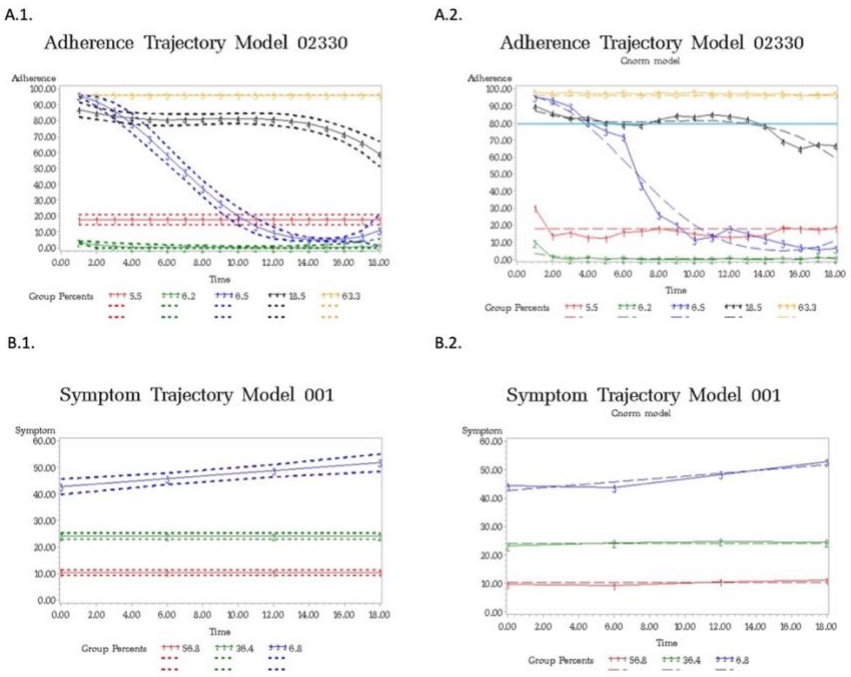
A.2. Probability of NSB group conditional on adherence group
impact of adherence on NSB

	Adherence Trajectory Group				
NSB Trajectory Group	Very low	Low	High/ sharp decrease	High/ slow decrease	Persistently high
Low/stable	.295	.470	.563	.365	**.662**
Moderate/stable	.580	.419	. 437	. 50	.293
Moderate/increasing	.126	. 112	0	.135	.044

A.3. Joint probability of NSB and adherence groups

	Adherence Trajectory Group				
NSB Trajectory Group	Very low	Low	High/ sharp decrease	High/ slow decrease	Persistently high
Low/stable	.016	.029	.032	.067	**.424**
Moderate/stable	.032	.026	.025	.092	.188
Moderate/increasing	.007	.007	0	.025	.029

Note: bolded results were mentioned in text.



Appendix Figure 2 Anastrozole Adherence (02330) and NSB (001) Trajectory Models

Note: Panel A1 is anastrozole adherence trajectory image with confidence intervals. Panel A2 shows the predicted (dashed) and actual (solid) trajectories and the solid horizontal aqua line at 80.00 marks 80% adherence. Panel B1 is the neuropsychological symptom burden trajectory image with confidence intervals. Panel B2 shows the predicted (dashed) and the actual (solid) neuropsychological symptom burden trajectories. Time points: pre anastrozole = 0.00; 6-months = 6.00; 12-months = 12.00; 18-months = 18.00; CNORM= censored normal; orders (shapes) of the trajectory lines name the models: 0=intercept, 1=linear, 2=quadratic, 3=cubic, e.g., 001= intercept, intercept, linear.

Appendix C Preliminary Work: Symptom Science: Omics Supports Common Biological Underpinnings Across Symptoms

Article

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Symptom Science: Omics Supports Common Biological Underpinnings Across Symptoms

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Abstract

For precision health care to be successful, an in-depth understanding of the biological mechanisms for symptom development and severity is essential. Omics-based research approaches facilitate identification of the biological underpinnings of symptoms. We reviewed literature for omics-based approaches and exemplar symptoms (sleep disruption, cognitive impairment, fatigue, gastrointestinal [GI] distress, and pain) to identify genes associated with the symptom or symptoms across disease processes. The review yielded 27 genes associated with more than one symptom. *ABCB1 (MDR1)*, *APOE*, *BDNF*, *CNR1*, *COMT*, *DAT1 (SLC6A3)*, *DRD4*, *ESR1*, *HLA-DRB1*, *IL10*, *IL1B*, *IL6*, *LTA*, *PTGS2 (COX-2)*, *SLC6A4*, and *TNF* were associated with cognitive impairment and pain, which had the most genes in common. *COMT* and *TNF* were related to all symptoms except sleep disruption. *IL1B* was associated with all symptoms except cognitive impairment. *IL10*, *IL1A*, *IL1B*, *IL1RN*, *IL6*, and *IL8 (CXCL8)* were linked with all the exemplar symptoms in various combinations. *ABCB1 (MDR1)* and *SLC6A4* were associated with cognitive impairment, GI distress, and pain. *IL10* and *IL6* were linked to cognitive impairment, fatigue, and pain. *APOE* and *BDNF* were associated with sleep disruption, cognitive impairment, and pain. The 27 genes were associated with canonical pathways including immune, inflammatory, and cell signaling. The pathway analysis generated a 15-gene model from the 27 as well as 3 networks, which incorporated new candidate genes. The findings support the hypothesis of overlapping biological underpinnings across the exemplar symptoms. Candidate genes may be targeted in future omics research to identify mechanisms of co-occurring symptoms for potential precision treatments.

Keywords

symptom, genomic, epigenomic, transcriptomic, review, pathway

Precision health care requires an understanding of the biological mechanisms underlying the development and severity of symptoms across disease processes. Such knowledge should also provide an explanation as to why some symptoms often co-occur in clusters. Omics approaches (i.e., genomics, epigenomics, and transcriptomics) have shown great promise for deciphering the biological underpinnings of symptoms,

Recently, there has been increasing support for research aimed at identifying those mechanisms underlying the development of symptoms and symptom clusters (Corwin et al., 2014; Miaskowski et al., 2017). Most of these studies have examined symptoms within the context of a chronic condition using an omics-based approach. However, very little has been done to either (a) assess support for associations between specific genes and a symptom in a disease-agnostic manner or (b) assess support for associations of specific genes across multiple symptoms.

The purpose of this manuscript was to review the literature related to omics and selected exemplar symptoms in a disease-agnostic manner, to identify genes associated with these symptoms, and then to determine which genes are associated with multiple symptoms. Our goal is to identify overlapping biological underpinnings across symptoms. We also sought to identify additional gene candidates for future evaluation based on biological relatedness to those genes associated with multiple symptoms.

Methods

We conducted a purposeful search of the literature in PubMed including all indexed publications prior to June 2017. Included articles had to be reporting on primary research with a

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quantitatively measured phenotype for the symptom of interest, have statistical analyses with the symptom as a dependent variable, and have significant findings (explicated in the manuscript) for the gene of interest, given our goal of identifying genes implicated in symptom phenotypes. We further limited search results to studies published in English and excluded reviews, meta-analyses, commentary, opinions, and non-data-based articles.

We selected symptoms for their relevance to the symptom science portion of the National Institute of Nursing Research (NINR) strategic plan and for their likelihood of co-occurrence across multiple disease processes (NINR, 2016). Thus, we selected the symptoms and search terms of "sleep disruption," "cognitive impairment," "fatigue" (excluding chronic fatigue syndrome), and "pain" (excluding acute coronary syndrome). We also wished to include the concept of gastrointestinal (GI) distress, but this entry did not yield results; therefore, we changed terms to reflect particular symptoms that are incorporated in GI distress: "nausea," "vomiting," "diarrhea," and "constipation" and refer to these as "GI distress" in this manuscript.

For each symptom, we queried on three different omic approaches: genomic, epigenomic, and transcriptomic. Search terms for genomics included the symptom search term and also "polymorphism," "genetic," OR "genomic." Similarly, the search terms for the epigenomic approach included the symptom search term and also "DNA methylation," "histone modification," "chromatin condensation," "epigenetic," OR "epigenomic." Finally, search terms for the transcriptomic approach included the symptom search term and also "gene expression" OR "transcriptome."

Symptoms were divided, so that each author screened abstracts for one symptom's relevant articles. If needed, they read the article to extract the necessary information or exclude the article. Many eliminated reports did not describe measurement of a symptom or analysis of the symptom directly. Many studies had a symptom listed as part of a larger phenotype, and several studies assessed a drug as treatment for the symptom rather than the symptom, itself.

We analyzed those genes that were significantly associated with more than one symptom using Ingenuity Pathway Analysis (IPA, QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis). IPA software allows for a variety of analyses and data interpretations by harnessing knowledge about biological pathways and interaction networks. We conducted the analyses using the Ingenuity Knowledge Base (genes only) as reference, considering both direct and indirect relationships. Network interactions included endogenous chemicals and were limited to 35 molecules and 25 networks. Node type excluded non-mammalians, and the data source excluded the Mouse Genome Database. Species was limited to humans, and no tissue lines were chosen. All mutations were considered. IPA produced an output with an interaction model of the 27 genes only, the most significant canonical pathways associated with the 27 genes, and the networks of molecules from the Ingenuity Knowledge Base that interact with the 27 genes.

Results

Cognitive impairment and pain symptoms were associated with the same genes more frequently than any other two symptoms (Table 1): *ABCB1 (MDR1)*, *APOE*, *BDNF*, *CNR1*, *COMT*, *DAT1 (SLC6A3)*, *DRD4*, *ESR1*, *HLA-DRB1*, *IL10*, *IL1B*, *IL6*, *LTA*, *PTGS2 (COX-2)*, *SLC6A4*, and *TNF*. *COMT* and *TNF* were related to all symptoms except sleep disruption. *IL1B* was associated with all symptoms except cognitive impairment. All of the symptoms investigated were associated with one or more interleukin genes (*IL10*, *IL1A*, *IL1B*, *IL1RN*, *IL6*, and *IL8/CXCL8*) in various combinations. Six genes had three symptoms associated with them: *ABCB1 (MDR1)* and *SLC6A4* (cognitive impairment, GI distress, and pain); *IL10* and *IL6* (cognitive impairment, fatigue, and pain); *APOE* and *BDNF* (sleep disruption, cognitive impairment, and pain); and *NTRK2* (sleep disruption, cognitive impairment, and fatigue). We present symptom-specific findings in Supplemental Tables A1–A5 along with table-specific references.

IPA

Relationships among the 27 genes that were associated with two or more symptoms are presented in Figure 1. Among these genes, seven had no known direct or indirect biological relationships with any other genes within the group: *CNR1*, *DRD3*, *HLA-DRB1*, *HTR1A*, *HTR3B*, *LTA*, and *SLC6A4*. The remaining 20 genes showed a direct or indirect biological relationship with at least one other gene to make three groupings: (1) the smallest interaction involved *BDNF* and *NTRK2*; (2) a three-gene interaction was noted for *DRD2*, *DRD4*, and *DAT1 (SLC6A3)*; (3) the main relationship model included the remaining 15 genes, mostly cytokines: *IL1A*, *IL1B*, *IL1RN*, *IL6*, *IL8 (CXCL8)*, *IL10*, *TNF*, *PTGS2 (COX-2)*, *CRP*, *OPRM1*, *COMT*, *ABCB1 (MDR1)*, *SIRT1*, *APOE*, and *ESR1*. All exemplar symptoms were represented in the main relationship model in various combinations.

Canonical Pathways

Next, IPA generated canonical pathways most significant to this list of 27 genes. From this query, we identified five different canonical pathways that overlapped with our gene list. Each of these pathways incorporated various interleukins, *TNF*, and additional genes from our model. The first pathway, *Altered T- and B-Cell Signaling in Rheumatoid Arthritis*, contained eight molecules from our model with major histocompatibility complexes. *Communication Between Innate and Adaptive Immune Cells* included eight molecules with *HLA-DR*. *Hepatic Cholestasis* contained nine molecules with *ESR1* and *ABCB1 (MDR1)*. *Role of Cytokines in Mediating Communication Between Immune Cells* included seven molecules, and *IL6 Signaling* consisted of eight molecules from our model with *ABCB1 (MDR1)* and *CRP* (refer to Supplemental Figures A1–A5 for canonical pathways).

Table 1. Associations in the Literature Between Genes and Selected Symptoms, with Methodological Approach.

	Symptom					Approach		
Gene	Sleep Disruption	Cognitive Impairment	Fatigue	GI Distress[a]	Pain	Genomic	Transcriptomic	Epigenomic
ABCB1 (MDR1)		√		√	√	**GI, P**	**C**	
APOE	√	√			√	**S, C, P**	**C**	
BACE1		√					C	C
BDNF	√	√			√	**S, C, P**	**C**	
CHRNA7		√				C	C	
CLOCK	√					S	S	S
CNR1		√			√	**C, P**		
COMT		√	√	√	√	**C, F, GI, P**		
CRP		√	√			**C**	**F**	
DAT1 (SLC6A3)		√			√	**C, P**		
DMN2		√				C	C	
DRD2		√		√		**C, GI**		
DRD3				√	√	**GI, P**		
DRD4		√			√	**C, P**		
ESR1		√			√	**C, P**		
FMR1		√				C	C	C
GHRL		√				C	C	
HAT Tip60	√					S		S
HLA-DRB1		√			√	**P**	**C**	
HTR1A				√	√	**GI, P**		
HTR3B				√	√	**GI, P**		
IL10		√	√		√	**C, F, P**	**P**	
IL1a				√	√	**GI, P**		
IL1B	√		√	√	√	**S, F, GI, P**	**P**	
IL1RN				√	√	**GI, P**		
IL6		√	√		√	**C, P**	**F, P**	
IL8 (CXCL8)			√		√	**F, P**		
KLOTHO		√				C		C
LTA		√			√	**C, P**	**P**	
MAPT		√				C	C	
NTRK2	√	√	√			**S, F**	**C**	
OPRM1				√	√	**GI, P**		**P**
PER2	√					S	S	
PER3	√					S	S	
PTGS2 (COX-2)		√			√	**C, P**		
SIRT1	√				√		**P**	**S**
SLC6A4 (5-HTTLPR)		√		√	√	**C, GI, P**	**C, P**	
SORL1		√				C		C
TNF		√	√	√	√	**F, P**	**C, GI, P**	**C**
TNFRSF1A		√				C	C	
TRPV1					√	P	P	P

Note. Bold text indicates that the gene has been associated in the literature with two or more symptoms. C = cognitive impairment; F = fatigue; GI = gastrointestinal; P = pain; S = sleep disruption.
[a]Please refer to text for terms used in GI distress search.

Networks

IPA generated networks from the 27 genes of interest by comparing them with a global molecular network from the Ingenuity Knowledge Base to identify connectivity among the molecules. We queried IPA with our list of 27 genes, and the resulting three networks each contained more than 3 of the 27 genes. The first network, *Organismal Injury and Abnormalities, Cardiovascular Disease, Nutritional Disease*, depicted in Figure 2, included 11 of the 27 genes of interest: *ABCB1 (MDR1)*, *BDNF*, *CNR1*, *IL8 (CXCL8)*, *DRD2*, *DRD4*, *LTA*, *NTRK2*, *OPRM1*, *PTGS2 (COX-2)*, and *DAT1 (SLC6A3)*. IPA scored this network at 22, indicating a high level of fit between our list of genes submitted and this network of molecules in IPA (Fisher's exact test of 1×10^{-22}) and a low probability of identifying this network by chance. Higher network scores indicate higher level of fit and are used to rank the networks of interest. All exemplar symptoms were represented in this network, and most of the molecules are involved in the *MAPK* signaling pathway.

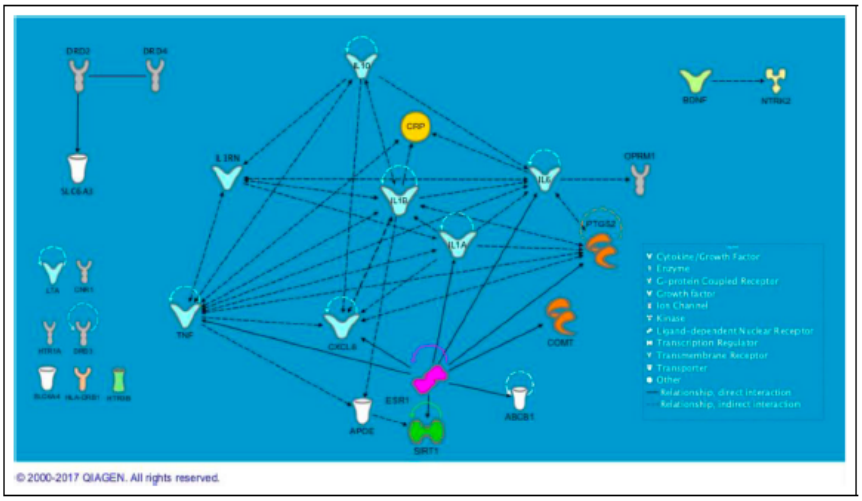

Figure 1. Relationships among genes associated with two or more symptoms. Ingenuity Pathway Analysis did not find relationships to others for the seven genes in the bottom left corner. Semicircles above genes indicate the gene's relationship with itself. For example, *ESR1* (estrogen receptor 1) inhibits and acts on itself, as indicated by the looped arrow, through many interactions. *ABCB1* = ATP-binding cassette subfamily B member 1 gene; *APOE* = apolipoprotein E gene; *BDNF* = brain-derived neurotrophic factor gene; *CNR1* = cannabinoid receptor 1 gene; *COMT* = catechol-O-methyltransferase gene; *CRP* = C-reactive protein gene; *CXCL8* = C-X-C motif chemokine ligand 8 gene; *DRD2* = dopamine receptor 2 gene; *DRD3* = dopamine receptor 3 gene; *DRD4* = dopamine receptor 4 gene; *ESR1* = estrogen receptor 1; *HLA-DRB1* = major histocompatibility complex, class II, DR beta 1 gene; *HTR1A* = 5-hydroxytryptamine receptor 1 alpha gene; *HTR3B* = 5-hydroxytryptamine receptor 3 beta gene; *IL1A* = interleukin 1 alpha gene; *IL1B* = interleukin 1 beta gene; *IL1RN* = interleukin 1 receptor antagonist gene; *IL6* = interleukin 6 gene; *IL10* = interleukin 10 gene; *LTA* = lymphotoxin alpha gene; *NTRK2* = neurotrophic receptor tyrosine kinase 2 gene; *OPRM1* = opioid receptor mu 1 gene; *PTGS2* = prostaglandin-endoperoxide synthase 2 gene; *SIRT1* = sirtuin 1 gene; *SLC6A3* = solute carrier family 6 member 3 gene; *SLC6A4* = solute carrier family 6 member 4 gene; *TNF* = tumor necrosis factor gene. Figures produced from IPA are available under an open-access CC-BY license for purposes of publication.

Interestingly, some other genes that surfaced during our review but were not linked to more than one symptom appeared in this network. For instance, *AKT1*, *CREB1*, and *RAS* group (*RAB5*, *RAB7*; Supplemental Table A2, Cognitive Impairment); *ERK (MAPK1)* and *MAPK* (Supplemental Table A5, Pain); and *NFkB* (complex; Supplemental Table A3, Fatigue). These findings indicate some additional biological support for these genes within the context of our exemplar symptoms, though associations between these genes and our chosen symptoms may not yet appear in the literature. Figure 2 also shows other genes/molecules that were included in this network but that we did not find to be associated with the exemplar symptoms in our review.

The second network, *Hereditary Disorder, Organismal Injury and Abnormalities, Respiratory Disease*, contained 8 of the 27 genes of interest: *APOE*, *CRP*, *IL6*, *IL10*, *IL1A*, *IL1B*, *IL1RN*, and *TNF*. In addition to the genes discussed in this review, this model includes *HLA-DR* as a group. Again, all symptoms of interest were included in this network (see Figure 3). The IPA network score was 14. Sod (*SOD1*) was linked to cognitive impairment but no other exemplar symptom (Supplemental Table A2, Cognitive Impairment). See Figure 3 for other prospective genes/molecules within this network that did not surface during our review.

The third network, *Hematological System Development and Function, Tissue Morphology, Cell-to-Cell Signaling and Interaction*, incorporated 4 of the 27 genes we found to be in common among the symptoms we investigated (see Figure 4): *COMT*, *ESR1*, *SIRT1*, and *SLC6A4*. The IPA score was 6 for this network. Other genes in this network that we found in our literature search to be associated with only one of the exemplar symptoms included *ERK 1/2* and *P38 MAPK (MAPK1)* in the pain review and *ESR2*, *Hsp70 (HSPA8)* *SHANK*, and *SOD1* genes from the cognitive impairment search. See Figure 4 for genes/substances not found in our review but included in the network.

These networks identified many additional genes that are known to be biologically related to the genes found during our

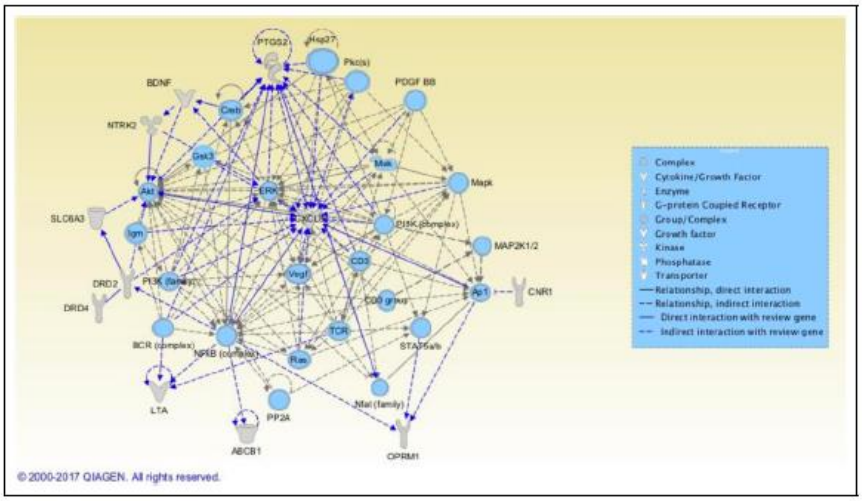

Figure 2. *Organismal Injury and Abnormalities, Cardiovascular Disease, Nutritional Disease* Ingenuity Pathway Analysis (IPA) Network. Genes colored gray are among the 27 genes we are exploring in this review; those colored blue have potential for future research. Bright blue relationships are drawn to or from the review genes to highlight relationships. (Readers viewing the paper version of this article are referred to the online version to view the figure in color.) Reviewed genes included in this network are *ABCB1* = ATP-binding cassette subfamily B member 1 gene; *BDNF* = brain-derived neurotrophic factor gene; *CNR1* = cannabinoid receptor 1 gene; *CXCL8* = C-X-C motif chemokine ligand 8 gene; *DRD2* = dopamine receptor 2 gene; *DRD4* = dopamine receptor 4 gene; *LTA* = lymphotoxin alpha gene; *NTRK2* = neurotrophic receptor tyrosine kinase 2 gene; *OPRM1* = opioid receptor mu 1 gene; *PTGS2* = prostaglandin-endoperoxide synthase 2 gene; *SLC6A3* = solute carrier family 6 member 3 gene. Figures produced from IPA are available under an open-access CC-BY license for purposes of publication.

review but that have not been investigated within the context of our exemplar symptoms to date.

Discussion

This literature review and the IPA analyses provide a glance into the burgeoning area of symptom science, which focuses on increasing our understanding of the biological underpinnings of symptoms using omics approaches. They also provide evidence that certain genes and biological pathways may underlie the biology of multiple symptoms, offering biological evidence explaining why some symptoms co-occur. Using the data generated from the review and a functional omics analysis tool (IPA), we could identify the biological pathways and networks associated with these genes that are currently supported by the literature as well as identify additional candidate genes for future investigations.

We found 27 genes in the literature that were significantly associated with development or severity of more than one symptom. Using IPA software, we found three groupings among the 27 genes. The first was a two-gene relationship between *BDNF* and *NTRK2*. (Descriptions of genes in this section were drawn from the *Genetics Home Reference* [U.S. National Library of Medicine, 2013] and *Online Mendelian Inheritance in Man*, 2017.) *BDNF* is a nerve growth factor thought to play a role in neuroplasticity and regulation of synapse transmission. *NTRK2* is involved in the *MAPK* pathway, plays a role in memory and learning, and is associated with obesity and mood disorders (*Online Mendelian Inheritance in Man OMIM®*, 2017; U.S. National Library of Medicine, 2013).

The second grouping was a three-gene interaction for *DRD2*, *DRD4*, and *DAT1 (SLC6A3)*. *DRD2* and *DRD4* have a direct interaction and inhibit adenylyl cyclase, which is needed to convert ATP to cAMP for energy production. *DRD2* is a G-coupling protein associated with locomotion, reward, reinforcement, and learning, and *DRD4* regulates emotion and behavior. *DRD2* also activates *DAT1 (SLC6A3)*, which encodes a dopamine transporter responsible for dopamine clearance.

In the third grouping, we found that 15 of the 27 genes have known direct or indirect biological relationships with each other. This grouping included genes representing all five of our symptoms of interest, further supporting common underlying biological processes across symptoms. *IL1A* and *IL1B* are proinflammatory cytokines, and the inhibitor of these genes

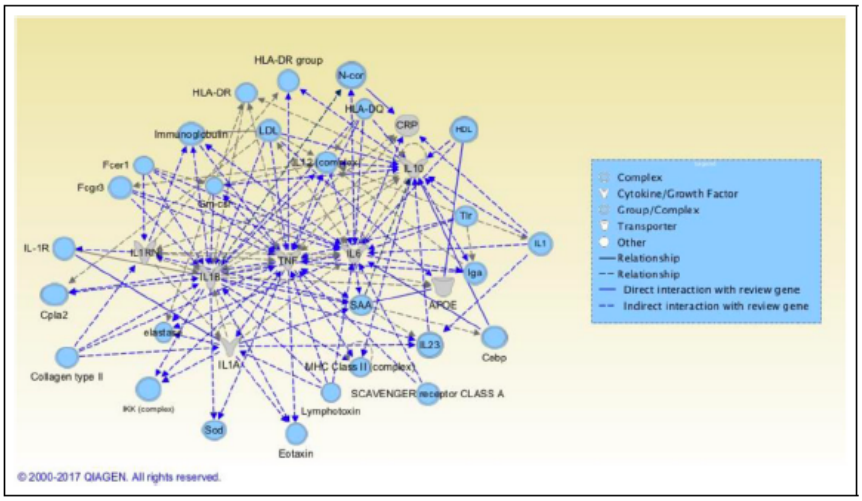

Figure 3. *Hereditary Disorder, Organismal Injury and Abnormalities, Respiratory Disease* Ingenuity Pathway Analysis (IPA) Network. Genes colored gray are among the 27 genes we are exploring in this review; those colored blue have potential for future research. Bright blue relationships are drawn to or from the review genes to highlight relationships. (Readers viewing the paper version of this article are referred to the online version to view the figure in color.) Reviewed genes included in this network are *APOE* = apolipoprotein E gene; *CRP* = C-reactive protein gene; *IL6* = interleukin 6 gene; *IL10* = interleukin 10 gene; *IL1A* = interleukin 1 alpha gene; *IL1B* = interleukin 1 beta gene; *IL1RN* = interleukin 1 receptor antagonist gene; *TNF* = tumor necrosis factor gene. Figures produced from IPA are available under an open-access CC-BY license for purposes of publication.

is *IL1RN*. *IL6* promotes B-cell maturation and inflammation. *IL8 (CXCL8)* is a chemokine that attracts neutrophils, basophils, and T cells. *IL10* regulates immunity and inflammation by inhibiting the synthesis of certain cytokines synthesis, including *TNF*. *TNF* is proinflammatory, secreted by macrophages, and involved in many processes including apoptosis, cell differentiation and proliferation, lipid metabolism, and coagulation. It is implicated in many inflammatory diseases. *PTGS2 (COX-2)* is a proinflammatory enzyme used to produce prostaglandins and its upregulation is linked to cancer, especially apoptosis resistance. *HLA-DRB1*, major histocompatibility complex II, binds with peptides from extracellular proteins and presents them on the surface of the cell for immune system recognition. It also plays a role in autoimmune disease. C-reactive protein (*CRP*) is part of the humoral immune response and reacts to foreign pathogens and damaged cells. *OPRM1* is an opioid receptor with roles in dopamine modulation. *COMT* inactivates catecholamines, including dopamine. *ABCB1 (MDR1)* transports molecules across cell membranes and the blood–brain barrier. *SIRT1*'s function is not clearly known, but the gene is thought to be involved in the stress response. *APOE* clears very-low-density lipoproteins and is known for its relation to Alzheimer's disease. Finally, *ESR1* encodes a receptor for estrogen. Estrogen and estrogen receptors are involved in sexual development, bone health, breast and endometrial cancers, and cardiovascular disease. In our model, *ESR1* appears in the center of several genes, which it directly influences *TNF*, *IL8 (CXCL8)*, *IL1A*, *IL6*, *PTGS2 (COX-2)*, *COMT*, *ABCB1 (MDR1)*, and *SIRT1*. These findings suggest a commonality among genes, symptoms, and disease processes.

Canonical pathways identified through IPA using common genes from our review primarily included immune, inflammatory, and cell-signaling pathways. From a disease perspective, it makes sense that these types of pathways would be significant. Most disease processes involve some degree of immune, inflammatory, and cell-signaling response, so the sharing of symptoms across these disease processes may indeed be linked to these mechanisms, which are common regardless of the disease specifics. For instance, heart disease (leading to myocardial infarction) and cancer have vastly different mechanisms of disease creation. But as both diseases progress, they create changes in the immune system, which trigger an inflammatory response and alterations in cell signaling (Deftereos et al., 2014; Hung et al., 2015). It is these changes that may help create those symptoms that are common to both (as in our exemplar symptoms here). Future work to decrease the impact

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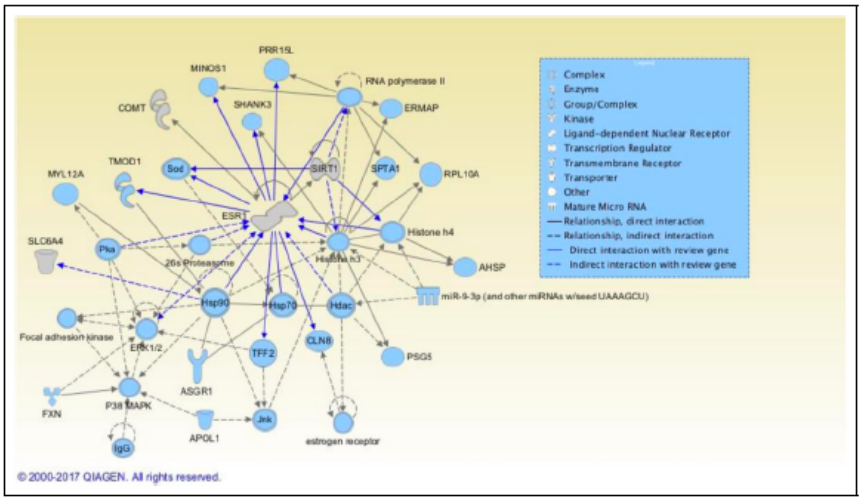

Figure 4. *Hematological System Development and Function, Tissue Morphology, Cell-to-Cell Signaling and Interaction* Ingenuity Pathway Analysis (IPA) Network. Genes colored gray are among the 27 genes we are exploring in this review; those colored blue have potential for future research. Bright blue relationships are drawn to or from the review genes to highlight relationships. (Readers viewing the paper version of this article are referred to the online version to view the figure in color.) Reviewed genes included in this network are *COMT* = catechol-O-methyltransferase gene; *ESR1* = estrogen receptor 1; *SIRT1* = sirtuin 1 gene; *SLC6A4* = solute carrier family 6 member 4 gene. Figures produced from IPA are available under an open-access CC-BY license for purposes of publication.

of these common symptoms should focus on regulating the changes that occur within these pathways that account for the common omic changes in the genetic pathways and networks presented here.

IPA generated three major networks of molecules from the Ingenuity Knowledge Base that interact with the 27 genes. The IPA scoring indicated that the networks have a very good fit. The lowest score (network 3) from the Fisher's exact test result was 1×10^{-6}, giving this network a one in a million chance of containing at least the same number of network-eligible molecules by chance when randomly choosing 35 molecules from the Ingenuity Knowledge Base. The other two networks are even less likely to have occurred by chance, at 1×10^{-22} (Network 1) and 1×10^{-11} (Network 2).

The first network, *Organismal Injury and Abnormalities, Cardiovascular Disease, Nutritional Disease*, contained 11 of the 27 genes. It also contained all exemplar symptoms, further supporting our hypothesis. Most of the molecules in this network are involved in the *MAPK*-signaling pathway. Genes in this network that had surfaced during our review but were not linked with more than one symptom were *AKT1* and *CREB1*, which affect cognition and memory; *RAS* (*RAB5*, *RAB7*), a proto-oncogene group linked with cognitive impairment (see Supplemental Table A2, Cognitive Impairment); *ERK (MAPK1)* and *MAPK*, which are associated with pain (see Supplemental Table A5, Pain); and *NFkB* (complex), which is linked with fatigue (see Supplemental Table A3, Fatigue). These findings provide some additional support for exploring these genes within the context of specific symptoms. Other genes included in the network but not found at all in our review are *AP-1*, activator protein-1, a transcription regulator; *BCR* (complex), a transmembrane receptor in the *MAPK* pathway; *CD3* group, signal transducers for T cells; *MEK*, mitogen-associated extracellular signal-related kinase in the *MAPK* pathway; *GSK3*, involved in glycogen metabolism; *Hsp27*, heat shock protein family B (small) member 1, part of the stress response; *IgM*, an immunoglobulin; Nfat (family), a group of transcription factors important for T cells; *PDGF BB*, platelet-derived growth factors; PI3K (family), lipid kinases; Pkc(s), a group of protein kinases; *PP2A*, protein phosphatase for negative control of cell growth and division; *STAT5a/b*, transcription factors; *TCR*, T-cell transmembrane receptor; and *VEGF*, a growth factor involved in angiogenesis.

The second network, *Hereditary Disorder, Organismal Injury and Abnormalities, Respiratory Disease*, included 8 of the 27 genes. Again, all exemplar symptoms were contained in this network. *IL1R*, which was only associated with pain in our review, came up in this network, as did Sod (*SOD1*), which

destroys free superoxide radicals and showed up in our cognitive impairment review. Other prospective genes/molecules within this network that did not surface during our review included *CEBPA*, a transcription factor that controls expression; collagen type II (COL2A1), important for connective tissues; Cpla2 (*PLA2G4A*), involved in hydrolysis of phospholipids; elastase, an enzyme; eotaxin, a chemokine; Fcer1, an IgE receptor; Fcgr3 (*FCGR3B*), an IgG receptor; Gm-csf (*CSF2*), a cytokine; IL23 (*IL23A*), which creates part of IL23 with IL12; IL12 (complex); immunoglobulin; *LDL*; N-cor (*NCOR1*); SAA, the serum amyloid apolipoproteins; scavenger receptor Class A, a group involved with lipoprotein uptake; and TLR, toll-like receptors that identify pathogens for the immune system (*Online Mendelian Inheritance in Man OMIM®*, 2017; U.S. National Library of Medicine, 2013).

Finally, the third network, *Hematological System Development and Function, Tissue Morphology, Cell-to-Cell Signaling and Interaction*, included 4 of the 27 genes. Genes/substances not found in our review but included in the network were 26S proteasome, a complex that removes damaged proteins; *AHSP*, a protein binder; *APOL1*, a high-density lipid involved in lipid exchange and transport; *ASGR1*, a transmembrane receptor; *CLN8*, a transmembrane protein in the endoplasmic reticulum; *ERMAP*, a transmembrane protein; focal adhesion kinase, which is involved in cell adhesion and motility; *FXN*, a mitochondrial protein; Hdac, the histone deacetylase family; histone h3 and histone h4; Hsp90, which assists with protein folding; IgG, an immunoglobulin; *Jnk (MAPK8)*; *MINOS1*, a protein binder; miR-9-3p, a microRNA that regulates post-transcription gene expression; *MYL12A*, which regulates smooth muscle and non-smooth muscle contraction; Pka group, protein kinases implicated in several cancers; *PRR15L*, part of the ATP family; *PSG5*, an immunoglobulin; RNA polymerase II, which is essential for transcription; *RPL10A*, a ribosomal protein; *SPTA1*, a scaffold postsynaptic density protein implicated in autism; *TFF2*, a scaffold protein of erythrocyte plasma membranes; and *TMOD1*, which also plays a role in shaping the erythrocyte membrane skeleton. While this network contained the fewest number of genes found in our review, the IPA score was still substantial, indicating a good fit for the network.

The combined evidence from the literature reviews, the IPA model, the linkage with canonical pathways, and the creation of IPA networks supports the hypothesis of overlapping biological underpinnings across exemplar symptoms. But there were some genes identified within these networks that were only associated with one symptom. There were also genes identified that have never been studied in relation to our selected exemplar symptoms. We believe these pathways and networks identify gaps in current literature and potential loci for future symptom omics research, which may help move symptom science forward.

While our results do have the potential for significant impact, our review and findings do also have some notable limitations. The first is the limitation of our exemplar symptoms. While we chose these specific exemplar symptoms on which to focus our review, other symptoms may have also added to the support. Our literature search was not exhaustive and was limited to PubMed. While PubMed includes most literature, there may be items published elsewhere that were not captured. Our findings may reflect publication bias because many of the omics approaches used were candidate approaches, therefore reflecting biases toward specific biological pathways thought to be involved in the development or severity of symptoms, as well bias introduced by limiting inclusion to only those articles with significant findings.

Conclusion

Nursing practice focused on symptom management should be based on evidence, including evidence supporting precision care for symptoms. Knowledge about the biological underpinnings for a symptom or co-occurring symptoms could aid in the identification of individuals at risk for symptom development or more severe symptom presentation as well as in treatment decisions and development of treatment interventions. Additionally, biological links between symptoms may indicate that treatment strategies could also be linked. In this article, we present current evidence provided by omics-based investigations that supports a role for biological pathways in symptom development and co-occurrence in a disease-agnostic manner.

Authors' Contribution

M. K. McCall contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. A. G. Stanfill contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. E. Skrovanek contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. J. R. Pforr contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. S. W. Wesmiller contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Y. P. Conley contributed to conception and design; contributed to acquisition, analysis, and interpretation of the data; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplementary material is available for this article online.

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Appendix D IRB Approval Letters

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Expedited)

Date:	August 28, 2019
IRB:	STUDY19050318
PI:	Maura Mccall
Title:	Trajectories and Predictors of Aromatase Inhibitor Adherence and Symptoms
Funding:	Name: Rockefeller University, Grant Office ID: FP00004873; Name: American Cancer Society, Grant Office ID: FP00003447, Funding Source ID: 133518_DSCN_19_049_01_SCN
Grant Title:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	8/28/2019
Expiration Date:	

Determinations:	None
Approved Documents:	• McCall Heilbrunn Application, Category: Sponsor Attachment; • McCall research plan 133518_DSCN_19_049_01_SCN, Category: Sponsor Attachment

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Dana DiVirgilio.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Pitt_510_EXP

University of Pittsburgh | Institutional Review Board
Office of Research Protections

APPROVAL OF SUBMISSION (Expedited)

Date:	June 2, 2021
IRB:	MOD19050318-001
PI:	Maura Mccall
Title:	Trajectories and Predictors of Aromatase Inhibitor Adherence and Symptoms
Funding:	Name: Rockefeller University, Grant Office ID: FP00004873; Name: National Cancer Institute , Grant Office ID: FP00004068, Funding Source ID: 1F99CA253771-01; Name: American Cancer Society, Grant Office ID: FP00003447, Funding Source ID: 133518_DSCN_19_049_01_SCN
Grant Title:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may continue as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Modification / Update
Approval Date:	6/2/2021
Expedited Category	(7)(b) Social science methods, (7)(a) Behavioral research

Determinations:	None
Approved Documents:	• Beck Depression Inventory II, Category: Other; • Breast Cancer Prevention Trial Checklist, Category: Other; • Brief Pain Inventory, Category: Other; • Economic Hardship, Category: Other; • Epworth Sleepiness Scale, Category: Other; • McCall F99 K00GrantApplication.pdf, Category: Sponsor Attachment; • Pittsburgh Sleep Quality Index, Category: Other; • Profile of Mood States, Category: Other

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Dana DiVirgilio.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

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