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Chemoprevention for Primary Breast Cancer Risk Reduction for Women at High Risk of Breast Cancer: Implementing an Evidence-Based Recommendation

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CHEMOPREVENTION FOR PRIMARY BREAST CANCER RISK REDUCTION FOR WOMEN AT HIGH RISK OF BREAST CANCER: IMPLEMENTING AN EVIDENCE-BASED RECOMMENDATION

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Has been approved as meeting the requirement for the Degree of Doctor of Nursing Practice in College of Natural and Health Sciences, School of Nursing, Program of Nursing Practice

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EXECUTIVE SUMMARY

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This capstone project was an evidence-based quality improvement project with three objectives: (a) to understand current practice of primary breast cancer chemoprevention in an integrated health system; (b) to evaluate the most current evidence available and the U.S. Preventive Services Task Force's (2013) *Breast Cancer: Medications for Risk Reduction* recommendation; and (c) to plan for implementation of the recommendation as a clinical practice guideline and evaluate the guideline outcomes through a future pilot study. The pilot study was not part of the capstone but included for planning purposes.

Evidence exists of the effectiveness of selective estrogen receptor modulators and aromatase inhibitors for risk reduction of primary breast cancer for women at high risk for the development of breast cancer. Recommendations have been published by national prevention and oncology organizations advocating use of these pharmacologic agents in the high-risk female population. Despite good evidence, the use of medications to prevent breast cancer among women at high risk has not been put into practice.

Local data support that women at high risk of breast cancer have not been educated about nor offered medications to reduce their risk. A Delphi method was used to understand obstacles to recommendation of chemoprevention and strategies to

facilitate discussions with high-risk women. The development and implementation of a clinical practice guideline for breast cancer risk reduction would increase use of current evidence consistent with national standards of care, inform women of options for breast cancer risk reduction, and engage healthcare providers in shared decision-making with women relevant to breast cancer risks.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
AE	Adverse Effects
AI	Aromatase Inhibitors
ASCO	American Society of Clinical Oncology
BCPT	Breast Cancer Prevention Trial
BCRAT	Breast Cancer Risk Assessment Tool (modified Gail Model)
B-RST	Breast – Referral Screening Tool
CPG	Clinical Practice Guideline
CHS	Complete Health Solutions (population health department at the healthcare system)
ER	Estrogen Receptor
HRT	Hormone replacement therapy
IBC	Invasive breast cancer
IBIS	International Breast Cancer Intervention Study
LCIS	Lobular Carcinoma in Situ
MAP.3	Mammary Prevention Trial, National Cancer Institute of Canada
MCO	Managed Care Organization
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NICE	National Institute of Health and Care Excellence (UK)
SERMs	Selective Estrogen Receptor Modulators
SME	Subject Matter Experts
STAR	Study of Tamoxifen and Raloxifene
USPSTF	U.S. Preventive Services Task Force

CHAPTER I

STATEMENT OF THE PROBLEM

Introduction

Breast cancer is a significant public health problem (Howell et al., 2014). Second only to skin cancers, breast cancer is the most common malignancy diagnosed in U.S. women (American Cancer Society [ACS], 2016b; DeSantis et al., 2015; Smith et al., 2015). In Colorado, breast cancer is the most commonly diagnosed cancer with 33.4% of diagnosed cancers attributable to the breast (Colorado Department of Public Health & Environment, 2016). For 2016, the ACS (2016b) estimates approximately 246,660 new cases of invasive breast cancer; 61,000 new cases of carcinoma in situ; and 40,450 breast cancer deaths among U.S. women. Only lung cancer causes more cancer deaths in U.S. women (ACS, 2016b; DeSantis et al., 2015). Women fear breast cancer due to familiar statistics such as one in eight or 12% of women will be diagnosed with invasive breast cancer in their lifetime (ACS, 2016b; DeSantis et al., 2015). Epidemiologists note the lifetime risk represents an average of risks of different women as breast cancer is not normally distributed in populations; most women have a low lifetime risk of less than 4% and the remaining women have risks from 4% to 80% (DeSantis et al., 2015; Evans et al., 2012).

Most women who develop breast cancer have no known risk factors beyond age and being female (ACS, 2016a; Genetic Home Reference, 2016). Subsets of women

have the highest risk for breast cancer. Association with familial breast or ovarian cancers accounts for approximately 15–20% of all breast cancers; of these, 5–10% are hereditary (ACS, 2016a). Information about risks might be particularly useful when making decisions about screening (Nelson et al., 2012) and advising women how to reduce their risk with lifestyle or pharmacologic modalities (Howell et al., 2014). Individuals with a family history of breast cancer might be at higher risk for breast cancer depending on presence of breast cancer in a first degree relative; number of relatives who had developed breast, ovarian, or a related cancer; age at which breast cancer was diagnosed in the relative; and age of the individual (ACS, 2016a; National Comprehensive Cancer Network [NCCN], 2016; National Institute for Healthcare Excellence [NICE], 2015). This increased risk is due to shared genetic and/or environmental risks.

Background and Significance

Katapodi, Dodd, Lee, and Facione (2009) revealed through a correlational cross sectional study of 184 English speaking women in a metropolitan setting on the western coast of the United States that most women underestimate their risk of breast cancer. Of women at high risk for breast cancer, 89% underestimated their actual risk (Katapodi et al., 2009). In a United Kingdom study assessing individual risk for diseases, 95% of women indicated they wanted to know their breast cancer risk (Evans et al., 2012). Many women at high risk might be eligible for risk-reducing interventions (Evans et al., 2012; Vogel, 2015).

There are evidence-based risk assessment strategies to identify women at higher than average risk for breast cancer (Nelson et al., 2012; NICE, 2015; Sestak & Cuzick,

2015; Tice et al., 2008; Tyrer, Duffy, & Cuzick, 2004). Use of these modalities, e.g., a clinical practice guideline (CPG) or a screening tool, to identify women at higher risk could allow for personalized care and education, interventions for prevention, early detection of disease, and decreased mortality (CRA Health, 2016).

Once identified, women who are at higher than average risk for the development of breast cancer could benefit from risk reduction strategies including preventive medical therapy commonly called chemoprevention. Surgical strategies such as prophylactic mastectomy and bilateral oophorectomy, although highly effective, were not addressed in this capstone. Freedman et al. (2003) estimated as early as 2003, as many as 15% of women age 35 to 79 might be eligible for tamoxifen chemoprevention. Howell et al. (2014) noted the risk and prevention panel involved in the Breast Cancer Campaign of 2012 estimated based on the relevant literature, nearly 50% of breast cancers could be prevented in women at high and moderate risk. Prevention of breast cancer in women at high risk could be achieved through the use of evidence-based preventive medications, specifically tamoxifen, raloxifene, exemestane, and anastrozole (Howell et al., 2014). Instructing all women in lifestyle measures including weight loss or limiting peri-menopausal and postmenopausal weight gain, regular exercise, and moderate consumption of alcohol could reduce breast cancer risk by approximately 30% (Howell et al., 2014). Additional health recommendations to reduce breast cancer included encouraging longer breastfeeding for overall health benefit to mother and baby, which might include a modest reduction of breast cancer risk in mothers (Howell et al., 2014).

As early as 1976, Sporn, Dunlop, Newton, and Smith of the National Cancer Institute in Bethesda coined the term “chemoprevention” as “the use of pharmacologic or

natural agents that inhibit the development of invasive cancer either by modifying 1) the initiation phase, or 2) the progression phase (otherwise known as the latent period or period of neoplasia)" (p. 1332). Cazzaniga and Bonanni (2012) expressed the current state of understanding risk-reducing medication:

> Although the precise mechanism or mechanisms that promote a breast cancer are not completely established, the success of several recent clinical trials in preventive settings in selected high risk populations suggests that chemoprevention is a rational and an appealing strategy. Breast cancer chemoprevention has focused heavily on endocrine intervention using selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). Achieving much success in this particular setting and new approaches as low-dose administration is actually under investigations in several topics. Unfortunately, these drugs are active in prevention of endocrine responsive lesions only and have no effect in reducing the risk of estrogen-negative breast cancer. Thus, recently new pathways, biomarkers, and agents likely are to be effective in this subgroup of cancers and were put under investigation. Moreover, the identification of new potential molecular targets and the development of agents aimed at these targets within cancer have already had a significant impact on advanced cancer therapy and provide a wealth of opportunities for chemoprevention. (Abstract)

A model of effective population risk reduction was found in cardiovascular health improvements by identifying individuals at risk and use of medications to reduce atherosclerosis and blood pressure (Howell et al., 2014). As with cardiovascular disease, treatment for breast cancer has improved over the past three decades, leading to reduced death rates for both diseases. Unlike cardiovascular disease, there is no direct feedback loop for breast cancer (Seidman, 2012). In cardiovascular disease treatment, blood pressures decrease and cholesterol levels decline with medication; there is no similar direct marker for breast cancer. Breast cancer deaths have decreased by nearly 33% over the past two decades (Howell et al., 2014). Despite this success, primary prevention of breast cancer has not been enacted at the population level as has occurred with cardiovascular disease (Howell et al., 2014).

Problem Statement

The following problem exists: women at increased risk for primary breast cancer due to strong family histories, genetic mutation, or personal atypical biopsies are not routinely and consistently being offered preventive therapy despite evidence that such therapy could reduce breast cancer by one quarter (Amir, Freedman, Seruga, & Evans, 2010) or by one-third to nearly 50% (Cuzick et al., 2014; Howell et al., 2014; Vogel, 2015). This capstone project evaluated current use of chemoprevention and queried subject matter experts (SMEs) regarding an evidence-based recommendation for use by clinicians in a large integrated managed care organization (MCO; Kaiser Permanente Colorado, 2016) to consider the use of pharmacological risk reduction interventions for women at high risk for breast cancer.

Chemoprevention Is Underused in Clinical Practice

The American Society of Clinical Oncology (ASCO; 2013) reviewers concluded:

> Research is needed to address the many unresolved issues related to the poor uptake of breast cancer chemoprevention agents in women who are at increased risk. These include (1) the design of effective tools and approaches to educate providers on the option of chemoprevention, (2) efficacious interventions that communicate to eligible women the risks and benefits of specific chemoprevention agents, (3) the development of tools that more accurately identify women at increased risk, and (4) a greater understanding of what disparities and barriers exist with regard to chemoprevention use among women at higher risk for breast cancer. (Visvanathan et al., 2013, p. 2960)

Many women are unaware of their personal risk for breast cancer (Vogel, 2015). The literature acknowledged difficulty in accurately identifying women at risk (Amir et al., 2010). For some individuals, family medical history is unknown. Murff, Spigel, and Syngal (2004) conducted a meta-analysis of 14 studies on family history of cancer and found the patient report of first degree family members with breast cancer was accurate at

about 80% with family members' medical history while the patient reported family history agreement with gynecologic cancers was significantly lower. Some family history was lost to present-day patients as people were reluctant to discuss their medical conditions, particularly those involving cancer (Domchek & Antoniou, 2007). Limitations of risk assessment tools for breast cancer, the tool's validation in populations, and limited discriminatory accuracy presented challenges to clinicians wanting to advise patients on chemoprevention (Amir et al., 2010).

Once identified as high risk for breast cancer through validated risk assessment models such as the National Cancer Institute's Breast Cancer Risk Assessment Tool (BCRAT--the modified Gail model; Gail et al., 1999), BRCAPRO (CRA Health, 2016), or the Tyrer-Cuzick (International Breast Cancer Intervention Study [IBIS]; Tyrer et al., 2004) model, women are not consistently and routinely informed of the availability of risk reduction interventions (Ozanne et al., 2013; Vogel, 2015). This issue is addressed in detail in this capstone.

Financial Impact: Cost of Breast Cancer Care

Costs for breast cancer care and treatment are substantial. Kaiser Permanente Colorado's (2016) partner in another geographic region with a larger population has been keen to identify women with a predisposition for breast cancer in order to offer genetic counseling for education and genetic testing, intensive surveillance, chemoprophylaxis, and surgical strategies for risk reduction. In the business case for comprehensive risk assessment screening of adult women, the Interregional Breast Cancer Leaders group projected a significant financial savings and quality of life improvement compared to usual care:

> Finding just the adult women carrying *BRCA* that we don't know about in our membership today will enable them to make choices to avoid 4,000 plus cases of breast and ovarian cancer allowing us to give $13,000 plus quality adjusted life years back to our members and their families. The benefit of this multidisciplinary approach is estimated to be $306 million NET from avoided cancer treatment costs. (S. Kutner, personal communication, October 15, 2015)

Challenges, Problems, Situations, and Opportunities Leading to the Capstone Project

If breast cancer in high-risk women can be reduced by up to 50% through medication for risk reduction, why is this clinical strategy not more widely embraced? Several reasons were exposed in the literature. Clinicians and health consumers fear health risks and adverse events from medications (Vogel, 2015). Patients perceive selective estrogen receptor modulator (SERM) risks to be greater than benefits as well as perceiving SERM side effects as greater than their personal risk of breast cancer (LaCroix et al., 2010). Patients fear endometrial cancer out of proportion to its true tamoxifen-related risk; there is no endometrial cancer risk with raloxifene (Vogel, 2015). The concept of probabilistic as compared to absolute risk is confusing (Malenka, Baron, Johansen, Wahrenberger, & Ross, 1993; Vogel, 2015). At-risk women make decisions for chemoprevention based on their lived experiences, which carry more weight than risk probabilities (Holmberg, Waters, Whitehouse, Daly, & McCaskill-Stevens, 2015). The experience of observing a loved one suffer through breast cancer treatment only to succumb to the disease might be a strong motivator to some women or a deterrent to screening and detection for others (Holmberg et al., 2015).

Ropka, Keim, and Philbrick (2010) reported healthcare providers have biases against use of medications for risk reduction of primary breast cancer. Lack of reasonably accurate and feasible methods for assessing personal individual risk and lack

of established risk thresholds that maximize benefit and minimize harms curtail wide spread use (Vogel, 2015). Menopausal hormone replacement therapy (HRT) is still widely used by post-menopausal women and cannot be used with a SERM (Vogel, 2015). The Patient Protection and Affordable Care Act of 2010 (Health and Human Services [HHS], 2015) required health insurance plans to cover counseling about chemoprevention for women at higher risk of breast cancer. Beginning January of 2014, SERM medication costs have been covered for chemoprevention of primary breast cancer in high-risk women (Sebelius & Wasserman Schultz, 2014).

Population estimates indicated as many as 15% of women age 35 to 70 years might be eligible for tamoxifen chemoprevention (Freedman et al., 2003). Complete Health Solutions (formerly Population and Prevention Services) of Kaiser Permanente Colorado lists 154,514 women ages 40 to 74 years enrolled as members in the health plan as of July, 2016 (A. Bayer, personal communication, July 15, 2016). Using Freedman et al.'s (2003) 15% estimate, roughly 23,177 women could be eligible for chemoprevention within the health system, which is an astounding number of women. Other studies suggested lower population estimates. An additional challenge was side effects to the medication limited their broad appeal. One quarter to 40% of trial participants discontinued chemoprevention due to adverse effects (Cuzick et al., 2013).

Factors Favoring Chemoprevention Uptake

Involvement in a clinical trial promotes primary breast cancer chemoprevention (Smith et al., 2016). Receiving a physician recommendation for risk-reducing medications is effective (Smith et al., 2016). The patient-perceived quality of clinician communication, such as having all questions answered by a physician, and perceiving the

clinician supported their understanding of risk-reducing therapy, is a significant predictor of uptake (Rondanina et al., 2008).

Clinicians want help with determining benefits and risks of risk reduction medications and how best to communicate these with women (Collins et al., 2014). Freedman et al. (2011) developed a risk/benefit index to facilitate patient education and shared decision-making regarding raloxifene and tamoxifen for postmenopausal women with and without a uterus. Their color-coded chart was designed to help providers select women in whose benefits from chemoprevention outweighed risks and, conversely, women in whom harms would restrict medication use. Education and support for all providers caring for women at higher risk for breast cancer is needed (Butow & Phillips, 2016). Recommendations for communication to patients include using absolute risk over relative risk estimates, i.e., "4 in 1000 women over 5 years will get a blood clot due to tamoxifen rather than tamoxifen doubles the risk of a blood clot" (Butow & Phillips, 2016, p. 554; Forrow, Taylor, & Arnold, 1992; Malenka et al., 1993). Heisey, Pimlott, Clemons, Cummings, and Drummond (2006) encouraged healthcare providers to utilize the term *risk reducing medication* rather than *chemoprevention* because it was less likely to lead women confusing these medications with cancer chemotherapy.

Limitations of Risk Reducing Medical Therapy for Women at High risk of Breast Cancer

Colditz, Wolin, and Gehlert (2012) summarized the critical barriers to change for the prevention of cancer in general. These could be applied to breast cancer:

(a) skepticism that cancer can be prevented,
(b) the short-term focus of cancer research,
(c) interventions deployed too late in life,
(d) research focus on treatment not prevention,

(e) debates among scientists,
(f) societal factors which affect health outcomes,
(g) lack of transdisciplinary approaches, and
(h) the complexity of successful implementation. (p. 127)

Despite data that document a decrease in incident breast cancer with SERMs and AIs, these prophylactic medications did not decrease breast cancer deaths based on 300,000 person years of follow up (Cuzick et al., 2013). The IBIS-1 revealed no differences in deaths between tamoxifen and placebo groups at a *p* value of 0.8 and non-statistically significant excess deaths in the tamoxifen arm 5.1% versus 4.6% at a *p* value of 0.4 (Cuzick et al., 2013).

Harms of Risk Reduction Medications: Life Threatening, Serious Events, and Other Events

Adverse effects (AEs) or toxicity of SERMs and AIs include life threatening effects and impacts on quality of life. Life-threatening effects of tamoxifen, raloxifene, exemestane, and anastrozole include stroke, pulmonary embolism, deep vein thrombosis (DVT), and endometrial cancer.

- Pulmonary embolus: Data from the National Surgical Adjuvant Breast and Bowel Study and the Breast Cancer Prevention Trial revealed an increase in pulmonary embolus among tamoxifen participants--risk ratio 3.01, 95% CI 1.15 -9.27 (Fisher et al, 1998); 1,449 women over 50 years of age would need to be treated to cause one case of pulmonary embolus (Mahoney, Bevers, Linos, & Willett, 2008, p. 355).
- Risk of venous thrombotic events (VTE) increased: tamoxifen relative risk (RR) 1.93 and raloxifene RR 1.60 (Nelson, Smith, Griffin, & Fu, 2013).

- Risk of endometrial cancer--tamoxifen RR 2.13. The number needed to harm (NNH) is 437 women older than 50 years who would need to be treated to cause one case of endometrial cancer (Mahoney et al., 2008, p. 355). Raloxifene RR is 1.14 (95% CI 0.65 – 1.98; Freedman et al., 2011).
- Increased risk for cataract development with tamoxifen use (risk ratio 1.14 95% CI 1.01-1.29; Fisher et al., 1998); 323 women would need to be treated with tamoxifen to cause one cataract (Mahoney et al., 2008).

Adverse events reported among placebo controlled trial participants included hot flashes (77.7% of users of tamoxifen versus 65% of placebo users, respectively); night sweats (66.8% versus 54.9%; Day et al., 1999); depression among 45%; insomnia; vaginal dryness (40% of users); and decreased libido (Vogel, 2015).

- Aromatase inhibitors worsened bone mineral density (Cuzick et al., 2014).

Overall, 25-40% of trial participants discontinued chemoprevention due to AEs. The pharmacogenomics of tamoxifen CYP2D6 enzyme metabolism indicated some women were poor metabolizers and other ultra-rapid metabolizers of the medication (Goetz, Kamal, & Ames, 2008). Not all women have the same response to therapy. Universal genetic CYP2D6 testing could make use of the SERM cost prohibitive. An agreement to recommend women test for pharmacogenomics could not be reached; a Food and Drug Administration Advisory Committee recommended indicating on the package insert that variability in metabolism occurs with the medication (Goetz et al., 2008).

- Aromatase inhibitors (AIs) block estrogen synthesis and are active only in post-menopausal women as the primary source of estrogen is conversion in

peripheral tissue as opposed to ovarian synthesis in pre-menopausal women (Mocellin, 2016).

- Overinflated stated benefits according to some researchers due to breast cancer overdiagnosis--a term for detection of non-significant, non-life threatening breast cancers noted due to aggressive screening programs (Prasad & Diener–West, 2015).

Theoretical Framework: The Stetler Model

The Stetler model (2001) is an evidence–based practice model used for project planning and implementation. It includes five phases and their purposes. The model is useful to describe translation of evidence into practice (Stetler, 2001). The model outlines steps of utilization of evidence to facilitate practice. The following steps were used to guide this capstone:

- Phase I: Preparation. This phase is comprised of project formulation, presentation of the capstone proposal to the capstone committee, and presentation to the Institutional Review Boards (IRB) of the healthcare organization (see Appendix A) and the university (see Appendix B).
- Phase II: Validation. This phase includes evaluating the literature on chemoprevention for breast cancer, comparing the integrated healthcare organization's experience with the literature, and using highest levels of evidence whenever possible, e.g., systematic reviews, meta-analysis, and randomized controlled trials (RCTs). Descriptive sources were also used as sources of evidence.

- Phase III: Comparative Evaluation/Decision Making. The Delphi method was used with subject matter experts to elucidate the obstacles and facilitators to implementation of chemoprevention and to develop a vision to overcome these barriers.
- Phase IV: Translation/Application. This phase includes developing and implementing a clinical practice guideline for primary breast cancer chemoprevention for high-risk women within the health system.
- Phase V: Evaluation (Stetler, 2001). This phase includes assessing the chemoprevention recommendation value to the organization, women members, and to healthcare providers, which will be done through a pilot study (not a part of the capstone).

Elements of Kaiser Permanente Colorado (the Organization) that supported evidence-informed practice included (a) leadership support; (b) the capacity to engage evidence-informed practice, specifically an effective implementation framework; and (c) infrastructure to support and maintain the culture of evidence-informed practice (Stetler, 2001). Key leadership for this work included the regional obstetrics and gynecology Value Advisor, the radiology department Value Advisor, the women's health governance council, the Breast Leaders group, and the Breast Cancer Screening Work Group (BCSWG). An implementation framework is in the planning stages in this project. The infrastructure to support and maintain evidence-informed practice is well established in the Organization as evidenced by the electronic clinical library and decision support tools for clinicians.

Literature Review

A comprehensive literature review undertaken to research the evidence included Cumulative Index to Nursing and Allied Health Literature (CINAHL), Elton B. Stevens Company (EBSCO), PubMed, Cochrane Database of Systematic Reviews, and Google Scholar™ for breast cancer chemoprevention. A search for a chemoprevention guideline within the health plan clinical library was undertaken. Keywords included breast neoplasm, breast cancer, risk screening, risk reducing medication, prevention of breast cancer, chemoprevention, primary breast cancer, women at high risk for breast cancer, and female. The focus was on high quality evidence from the current and past five years with inclusion of important earlier RCTs, systematic reviews, and descriptive studies to complement the evidence related to this capstone.

Clinical Practice Recommendation

The U.S. Preventive Service Task Force (USPSTF) *2013 Breast Cancer: Medications for Risk Reduction* endorsed clinicians' engagement with women at increased risk for breast cancer regarding use of tamoxifen and raloxifene to reduce their risk of breast cancer. Nelson et al. (2013) designated this recommendation Grade B evidence, indicating there was a high degree of certainty that the net benefit would be moderate or a moderate certainty that the net benefit would be moderate to substantial (see Appendix C).

The USPSTF (2013) recommended primary care providers screen all women patients with any family history of breast, ovarian, tubal, or peritoneal cancer with one of several simple screening tools as a first step in identifying the need for genetic counseling and possible genetic testing for BRCA1 or BRCA2 deleterious genes (Moyer, 2014).

The target population for screening is asymptomatic women 35 years of age and older *without* a history of breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS; Moyer, 2014).

The Breast Referral Screening Tool (B-RST; Bellcross, Lemke, Pape, Tess, & Meisner, 2009) is an easy to use electronic questionnaire that Traxler et al. (2014) demonstrated public health nurses could incorporate into screening. On average, this screening added five minutes to the nurse's care encounter (Traxler et al., 2014). The screening calculates a negative result (not at increased risk for a genetic mutation contributing to breast cancer) or a positive finding (a 5-10% chance or greater of having a genetic mutation contributing to breast cancer). Positives are then referred to a genetics counselor for a more thorough assessment of risk and possible genetics testing for BRCA1, BRCA2, PTEN, TP53, and potentially other deleterious genetic mutations (Traxler et al., 2014). The screening program is readily available on-line in open access (Emory University, 2012).

A commonly-used population screening tool is the modified Gail model (now referred to as the NCI's Breast Cancer Risk Assessment Tool [BCRAT]) for identification of women who might be at higher than average risk for breast cancer (Constantino et al., 1999). A calculated risk of 1.66% or greater for breast cancer in the next five years would indicate increased breast cancer risk above the population risk (Howell et al., 2014, Nelson et al., 2013; USPSTF, 2013). Due to medication toxicity risk, USPSTF (2013) cautiously advised preventive treatment based on a 3% five-year risk instead of the 1.66% (Howell et al., 2014; Nelson et al., 2013). Risk/benefit tables developed by Freedman et al. (2011) were developed to guide determination of

medication use based on age, race or ethnicity, and hysterectomized status of the woman (Howell et al., 2014).

The USPSTF (2013) recommended use of

- Tamoxifen when benefits are greater than risks for women 50-59 years of age whose estimated five-year risk of invasive breast cancer is 4.5% or greater (determined by BCRAT; NCI, 1999; Nelson et al., 2013; Vogel, 2015).
- Raloxifene when benefits are greater when estimated five-year risk according to the BCRAT is
    - greater than 2% among women in their 50s,
    - 3% among women in their 60s, and
    - 4% among women in their 70s (Nelson et al., 2013; Vogel, 2015).

Primary prevention trials with placebo controls indicated tamoxifen and raloxifene reduced the incidence of invasive breast cancer by seven to nine cases per 1,000 women over a five-year treatment period (Nelson et al., 2013). Individuals with the highest risk derived the most benefit with the two SERMS (Nelson et al., 2009).

Oncology organizations support the USPSTF (2013) recommendation. The American Society of Clinical Oncology (ASCO; 2013) guideline recommended women 35 years or older with a five-year breast cancer risk greater than 1.67% discuss as an option the use of tamoxifen, raloxifene, and exemestane to reduce the risk of estrogen receptor (ER)-positive breast cancer. The ASCO's report included a systematic review of randomized controlled trials and meta-analysis published between 2007 and 2013, encompassing 19 trails and six risk reduction medications (Visvanathan et al., 2013):

- Specifically, ASCO recommended high-risk women age 35 or older be advised of the option of tamoxifen 20 mg per day for five years to reduce the risk of ER-positive breast cancer.
- For post-menopausal women, raloxifene 60 mg per day for five years and exemestane 25 mg per day for five years should be discussed as options for breast cancer risk reduction (Howell et al., 2014).
- High risk is defined as individuals with a five-year projected absolute risk of breast cancer of more than 1.66% (based on the BCRAT or equivalent measure) or women diagnosed with lobular carcinoma in situ (Howell et al., 2014).
- Selective estrogen receptor modulators are contraindicated in women with a history of DVT, pulmonary embolus, stroke, or transient ischemic attack, or during prolonged immobilization, or in combination with HRT (Howell et al., 2014).

The United Kingdom National Institute of Health and Care Excellence (NICE; 2015) guideline for women at increased risk of breast cancer by virtue of family history of disease recommended that women with a greater than 30% lifetime risk (1 in 3-4+) of breast cancer be offered tamoxifen or raloxifene and those with a greater than 17% (1 in 6+) lifetime risk should consider preventive therapy. Aromatase inhibitors were not endorsed at the time of their guideline publication (IBIS-II was not yet published) but NICE did advise a lifestyle handout be provided (Howell et al., 2014).

The National Comprehensive Cancer Network (NCCN; 2016) published guidelines for breast cancer risk reduction; it acknowledged the difficulty of estimating breast cancer risk for an individual. Women and their healthcare providers must weigh demonstrated benefits with health risks of the interventions--surgical strategies such as bilateral mastectomy or, in some cases, bilateral oophorectomy. Chemopreventive interventions include SERMs and AIs. The NCCN recommends use of the modified Gail model (BCRAT) to assess breast cancer risk in women 35 or older:

> Women determined to be at increased risk for breast cancer with a life expectancy of ten or more years should have counseling, specific to the individual, to reduce breast cancer risk. Risk reduction surgery is recommended for *BRCA1* and *BRCA2* mutation carriers and risk reduction medications are recommend for individuals without contraindications to the medication. (MS-6)

The NCCN (2016) recommends tamoxifen as a superior choice of risk reduction for most postmenopausal women who want non-surgical approaches to lower their breast cancer risk. Subject matter experts (Vogel et al., 2010) concluded tamoxifen had continued risk reduction after cessation of therapy whereas raloxifene showed diminished benefits. Results of the Breast Cancer Prevention Trial (BCPT; Fisher et al., 1998), indicated a subpopulation of women with atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS) had significant benefits outweighing risks with tamoxifen. The NCCN experts on the Breast Cancer Risk Reduction Panel *strongly recommended* chemoprevention for these women. It was recommended that high quality evidence from randomized controlled trials (RCTs) be used when counseling high risk women on the risks, benefits, and alternatives to risk-reduction medications—e.g., information from the BCPT, the study of tamoxifen and raloxifene (STAR), Mammary Prevention 3 (MAP.3; Goss et al., 2011), and IBIS-II trials (Cuzick et al., 2014; NCCN, 2016).

Based on findings from the BCPT (Fisher et al., 1998), the U.S. Food and Drug Administration (FDA) approved tamoxifen in 1999 for breast cancer risk reduction for women at high risk (NCCN, 2016). In 2007, the FDA approved raloxifene to reduce risk of invasive breast cancer in postmenopausal women with osteoporosis or high risk of invasive breast cancer (Freedman et al., 2011). In January 2014, the U.S. Department Health and Human Services announced tamoxifen and raloxifene as covered benefits by insurance plans without individual copayment for primary breast cancer risk reduction in women at increased risk for breast cancer with low risk of adverse effects (Sebelius & Wasserman Schultz, 2014).

The American Cancer Society (ACS) guidelines for cancer prevention were published in 2010 (Kushi et al., 2012). Four lifestyle recommendation were endorsed to reduce cancer risk overall: (a) achieve and maintain a healthy weight throughout life, (b) keep a physically active lifestyle, (c) consume a healthy diet, emphasizing plant foods, and (d) limit consumption of alcoholic beverages. All women are advised to follow these recommendations to lower cancer risk.

Synthesis of the Literature

The literature supported the recommendation for appropriate high risk women be informed and consider use of risk-reduction strategies to prevent breast cancer. Randomized controlled trials indicated SERMs (tamoxifen or raloxifene) or AIs (exemestane or anastrozole) lower risk of primary breast cancer (Amir et al., 2010; Cuzick et al., 2013; Goss et al., 2011; Nelson et al., 2013). In SERM trials, 83,399 participants were followed over an average period of 65 months with 306,617 years of follow up (Howell et al., 2014). The aggregate reduction in all breast cancer, including

DCIS, with tamoxifen 20 mg per day was 38% ($p < 0.001$; Cuzick et al., 2013). Trial data suggested an estimated 10 year decrease in cumulative incidence from 6.3% in the control group to 4.2 % in the SERM groups (Howell et al., 2014). In the STAR trial, tamoxifen was superior to raloxifene in longer term follow-up for prevention of invasive breast cancer (relative risk of raloxifene to tamoxifen 1.24, 95% confidence interval 1.05-1.47; Fisher et al., 1998; Vogel et al., 2010). Raloxifene contributed fewer side effects than tamoxifen, particularly for women with a uterus, and some researchers suggested raloxifene is preferable in post-menopausal women (Freedman et al., 2011; Howell et al., 2014).

A recent meta-analysis of risk-reducing medications for incident breast cancer published in the *Cochrane Database of Systematic Reviews* validated that the aromatase inhibitors exemestane and anastrozole were effective in primary prevention of breast cancer in post-menopausal women (Mocellin, 2016). Placebo-controlled trials of exemestane reported a 65% reduction of breast cancer risk after five years of treatment (Goss et al., 2011). The IBIS-II study (Cuzick et al., 2014) compared anastrozole to placebo; 3,864 post-menopausal women 40 through 70 years of age at increased risk of breast cancer were randomly assigned to anastrozole one milligram per day or placebo for five years. The incidence of breast cancer declined by 53% in anastrozole users (hazard ratio 0.47, 95% CI 0.32 to 0.68; Cuzick et al., 2014). Health risks of aromatase inhibitors did not include thromboembolic risk and endometrial cancer; yet they were associated with mild to moderate myalgia and arthralgia and reduced bone density (Cuzick et al., 2014; Howell et al., 2014).

Waters, Cronin, Graubard, Han, and Freedman (2010) estimated only 2% of eligible women opt for chemoprevention. A systematic review of uptake of primary breast cancer chemoprevention in 26 studies encompassing 21,423 women revealed higher utilization in clinical trials (25.2%, 95% confidence interval [CI] 18.3-32.2) than in non–trial settings (8.7%, 95% CI 6.8-10.9). The pooled uptake estimate was 16.3%, 95% CI 13.6-19.0 (Smith et al., 2016).

The largest risk reduction in breast cancer occurs in the first five years (Cuzick et al., 2013) and the duration of benefit might last 20 years (Butow & Phillips, 2016; Smith et al, 2016). Cuzick and colleagues (2013) reported the number needed to treat (NNT) to prevent one case of incident breast cancer is 40-60. Vogel (2015) cited a NNT of 42 to prevent one incidence of breast cancer using data in the same meta-analysis.

Among women at highest breast cancer risk with BRCA 1 and BRCA 2 gene mutations, tamoxifen decreased risk among women with BRCA 2 by 62 % (Fisher et al., 1998; King et al., 2001) with no effect among BRCA 1 mutation carriers who are more likely to develop ER-negative neoplasms (Goss et al., 2011; Stuckey & Onstad, 2015). Although evidence indicated SERMs and AIs could reduce the incidence of primary breast cancer, data are lacking that risk reduction by SERMs or AIs reduces breast cancer deaths (Moyer, 2014; Nelson et al., 2013; Visvanathan et al., 2013).

Freedman et al. (2011) developed a risk-to-benefit index to quantify benefits from chemoprevention with tamoxifen or raloxifene for breast cancer prevention in post-menopausal women. This benefit to risk index complemented clinical evaluation for decision-making for initiation of chemoprevention. The indices were based on

background risks in populations of White, Black and Hispanic women 50 years of age and older with and without a uterus (Freedman et al., 2011).

Summary

Not all women have equal risks for the development of breast cancer. Women identified as high risk for breast cancer are best served by a comprehensive patient-centered discussion with a healthcare provider knowledgeable in appropriate surveillance and risk reduction strategies. Randomized controlled trials, systematic reviews, and meta-analysis of RCTs provide high quality evidence of the effectiveness of tamoxifen, raloxifene, exemestane and anastrozole for primary breast cancer risk reduction in women at increased risk of breast cancer. A weakness of current processes is a perceived lack of knowledge among women and their care providers about risk reduction medications. Additionally, a gap in care exists with the low uptake of these medications in women who could benefit.

CHAPTER II

PROJECT DESCRIPTION

Purpose of the Doctor of Nursing Practice Project

The purpose of this Doctor of Nursing Practice (DNP) capstone project was to assess the current state of chemoprevention for women at high risk of breast cancer at the managed care organization and the evidence and applicability of the 2013 USPSTF recommendation to discuss and offer medications for breast cancer risk reduction as well as design a pilot study to implement the recommendation based on subject matter experts' consensus.

Project Objectives

1. Obtain baseline information on the current use of chemoprevention for high-risk women at Kaiser Permanente Colorado (the Organization).
2. Evaluate the most current evidence available and the U.S Preventive Service Task Force's (2013) *Breast Cancer: Medications for Risk Reduction* recommendation and its applicability to the population in the managed care setting.
3. Plan how to implement the recommendation as a clinical practice guideline and evaluate the guideline outcomes through a pilot study.

Objective One

Data from pharmacy records from September 1, 2015 through September 20, 2016 were gathered utilizing International Classification of Disease (ICD) codes. The ICD-10 and ICD–9 codes were used as the year under evaluation included the time of transition from ICD– 9 to ICD-10 in October 2015 (see Table 1). There were 37 prescriptions for tamoxifen, raloxifene, exemestane, and anastrozole for women without a current or past diagnosis of breast cancer. This number of prescriptions provided the baseline. The author acknowledges the limitation of this process; despite steps to isolate prescriptions specifically for women who do not have cancer currently or a past diagnosis, women taking these medications for prevention of recurrent disease might have been included in this baseline number. Additional baseline data were obtained through the author's pilot survey of women members at a specific obstetrics and gynecology group practice within the Organization.

Table 1

International Classification of Disease Codes Indicative of Women Taking Risk-Reducing Medications for Primary Breast Cancer at Kaiser Permanente Colorado

Diagnosis	ICD-9 code	ICD- 10 code	Number of prescriptions
Family history of malignant neoplasm of breast	V16.3	Z80.3	7
Genetic susceptibility to malignant neoplasm of breast	V84.01	Z15.01	1
a) BRCA 1gene mutation positive			3
b) BRCA 2 gene mutation positive			3
Family history of carrier of genetic disease		Z84.81	None found specific to this code
Lobular carcinoma of breast in situ of unspecified breast		D05.00	0
Lobular carcinoma in situ of right breast		D05.01	1
Lobular carcinoma in situ of left breast		D05.02	3
Atypical ductal hyperplasia (ADH)	610.8	610.8x Atypical ductal hyperplasia unspecified	None found specific to this code
Atypical ductal hyperplasia, right breast		610.1x	9
Atypical ductal hyperplasia left		610. 2x	9
High risk for development of breast cancer (nonspecific) (Fine, Gittleman, & Kobbermann, 2015)	611.9	N64.9	None found
Personal history of therapeutic irradiation		Z92.3	None found
Family history of ovarian cancer		Z80.41	1
Total RX			**37**

Other ICD-10 codes: Z80.41, Z80.49, Z85.3, Z85.43
(Codes largely obtained from Fine et al., 2015; www.icd10data.com; prescriptions at KPCO from T. Delate, personal communication, September 22, 2016).

The Organization's breast cancer screening clinical practice guideline (Williams, 2013) recommended performing a risk assessment for all women beginning at age 40 and repeating at least every five years. Similar to the BCRAT model (NCI, 1999) and the B-RST (Emory University, 2012), the guideline asks about personal and family history of breast cancer. A convenience sample of 200 women was screened using the MCO's clinical practice guideline for risk assessment; the lower age range was moved to 30 to identify young women who might have risk factors. The guideline (Williams, 2013) defined high risk as

- Personal history of breast cancer including lobular and DCIS
- Breast biopsy showing atypical hyperplasia, atypical apocrine metaplasia, or lobular hyperplasia (LCIS)
- A first degree relative of either sex (parent, sibling or child) diagnosed with breast cancer
- Documentation of an inherited genetic alteration associated with increased breast cancer risk
- Blood relative with documentation of an inherited genetics alteration associated with increased breast cancer risk.

The Breast Cancer Screening Work Group added women who had had mantle field chest irradiation at age less than 30 for Hodgkin's lymphoma as a high risk group as these individuals' risk for breast cancer was substantially higher than the general population (ACS, 2016a; NCCN, 2016). This risk factor was added to the questionnaire.

Of 200 women screened, 56 women (28% of the sample) indicated at least one of the above risk factors. Five of the 200 women (2.5%) had a prior or current diagnosis of

breast cancer. If these five women were excluded, 25.5% of the group (51 women) indicated some factor that could increase their risk. Upon review of the women's responses, six women were referred to adult genetics for counseling and determination of fit for genetic mutation carrier testing. These six women comprised 3% of the group surveyed and 10.1% of those with any positive screening response. Eleven women of the 200 had previously been referred to hereditary cancer genetics.

Objective Two

A literature review was done using CINAHL, Pub Med, EBSCO Host, Cochrane Database of Clinical Trials, and Google Scholar™. High quality and high level evidence was sought, specifically systematic reviews or meta-analyses of randomized controlled trials (RCTs) for use of medications to reduce primary breast cancer risk. Other levels of evidence obtained and reviewed included well-designed RCTs--level II, well-designed controlled trials without randomization--level III, well-designed observational cohort studies--level IV, descriptive and qualitative studies--level V, and expert opinion--level VI (Melnyk & Fineout-Overholt, 2015, p. 92). Focus on the literature was from the past five years with inclusion of important guiding research from earlier dates.

A Delphi survey was undertaken to ascertain subject matters experts' (SMEs) opinions on chemoprevention of primary breast cancer for high-risk women in the population of adult women at the integrated health system. The findings from the Delphi survey comprised the strategy for development of a clinical practice guideline (CPG) for the Organization. A pilot study is planned to evaluate the outcomes of the clinical practice guideline (not actually undertaken for this capstone).

Objective Three

A Delphi survey in two rounds was undertaken to ascertain subject matter experts' opinions on chemoprevention of primary breast cancer for high risk women in the population of adult women at Kaiser Permanente Colorado. The findings from the Delphi surveys were incorporated into the clinical practice guideline (CPG) along with the evidence from the literature (see Appendix G). The Guideline for Risk-Reducing Medication for Women at High Risk of Breast Cancer is designed to facilitate counseling and prescribing chemoprevention. Included in the guideline are identification of appropriate high risk women, evidence about risks/benefits and alternatives to risk reducing medications, resources for education of women, and direct orders for consultation and medication. The guideline will be reviewed for approval for the clinical library by members of the Women's Health Quality Council. A pilot study is planned to evaluate the outcomes of the clinical practice guideline (not actually undertaken for this DNP project).

Evidence-Based Project Intervention Plan

In the literature, high risk is consistently defined as a five-year risk breast cancer of 1.67% or greater or a lifetime risk of breast cancer of 20% or greater from the BCRAT (NCI, 1999; USPSTF, 2013) or other research risk assessment tools. Women identified as high risk were offered additional screening as appropriate using NCCN (2016) guidelines and were invited to discuss risk reduction strategies. For this project, a Delphi survey was utilized to build consensus about offering risk reduction medication for women at high risk for breast cancer.

Project Design and Method

This DNP project sought to put best evidence into practice and was non-experimental. No patients were directly involved and no personal health information was used in this project. Demographic data and opinions from healthcare providers regarding chemoprevention for women at high risk for breast cancer were gathered through two Delphi survey rounds. The Delphi method was selected as it has been used effectively to gather consensus where the literature is incomplete or the best approach is unknown (Hasson, Keeney, & McKenna, 2000). Participants from various medical and nursing disciplines as well as pharmacy were selected to represent a cross-section of subject matter experts who care for women within the healthcare organization. The questions were formulated to seek consensus at a level of 70% regarding the challenges to chemoprevention and strategies to overcome barriers.

Awareness of women at high risk for breast cancer and mechanism of risk determination was necessary for this project's implementation and success. Traxler et al. (2014) implemented a population-based risk assessment of breast cancer in public health clinics in Georgia. The authors aimed to address disparities in screening of African American women. Women with risk factors suggesting increased breast cancer risk were contacted by a genetic counselor to further clarify risk and offer education and testing as appropriate. In the population, 6% of women met criteria for referral to genetic counseling (Traxler et al., 2014). Shah et al. (2012) implemented a risk assessment in a hospital-based health system to identify women at high risk at the time of mammography. Of 5,878 women who had a breast cancer risk assessment, 17% screened high risk according to the BCRAT (NCI, 1999; Shah et al., 2012). The authors noted incorporation

of screening for breast cancer risk could be easily and efficiently added to screening mammography. Once identified, these individuals could be offered more personalized surveillance and prevention (Shah et al., 2012). The healthcare organization is taking steps to provide risk members with the introduction of a software tool in radiology later this year (Kaiser Permanente, 2016).

Despite the published guideline within our health system, women have not routinely been assessed for breast cancer risk factors (Williams, 2013). This problem is not unique to our health system; others (Phillips et al., 2016; Shah et al., 2012; Traxler et al., 2014) have sought creative solutions to perform risk assessments in primary care and radiology, respectively, to identify women at higher than average risk.

In the United Kingdom, a study was undertaken to assess individual risk for breast cancer in comparison to an age-based population screening mechanism (Evans et al., 2012). Of the population of 10,000 women who consented, 1.07% (107 women) screened high risk by the Tyrer–Cuzick tool (also known as the IBIS risk assessment; Tyrer et al., 2004). The study authors found it feasible to determine breast cancer risk and make decisions upon risk in the context of a population–based mammography screening (Evans & Howell, 2015). If applied to women in the 40 to 74-year-old range at the integrated MCO where this capstone project occurred, 1.07% of 154,514 suggests 1,653 women would be high risk. The literature acknowledged the BCRAT overestimates risk and the Tyrer-Cuzick model underestimates risk as reproductive and family and personal history are handled differently in these two models. Butow and Philips (2016) are currently developing an online tool labeled iPrevent to facilitate

personalized risk calculation using established validated algorithms and communication (paper under review).

Congruence with Organization's Strategic Plan

This evidence-based quality improvement project was undertaken at an Organization that focuses on population health (Kaiser Permanente). Prevention of disease is a primary goal for the community of members. The mission of the Organization is "to provide high –quality, affordable health services and to improve the health of our members and the communities we serve" (Kaiser Permanente, 2016, para. 2). The vision of the Organization is "to be a leader in Total Health by making lives better" (Kaiser Permanente, 2016, Our Vision). The strategic plan includes maintaining competitiveness in the healthcare marketplace, controlling costs, and meeting member's health care quality and service needs while ensuring a highly competent work force (S. Martinez, personal communication, May 12, 2016). The Organization's value compass places the member (patient) in the center with *spokes* for best quality of care, most affordable, best service, and best place to work. Specific women's health goals for 2016 include improvement in patient satisfaction scores as a measure of service and maintenance of per member/per month (PMPM) costs. This capstone project might improve patient satisfaction through the inclusion of personalized breast health as part of comprehensive women's care. Affordability might ultimately be improved with breast cancer risk assessments in contrast to age-based breast cancer screening if, over the long run, risk awareness leads to prevention and early detection or disease. The Organization's partner in another region submitted a business case for risk-based

screening with projected cost savings over the current state of care (S. Kutner, personal communication, October 15, 2015).

Timeline of Project Phases

- Phase 1 Preparation:
  - Topic identified--September, 2015
  - Capstone committee formed--October, 2015
  - Capstone committee approved--December, 2015
  - Capstone proposal approved--December, 2015
- Phase II Validation: Literature search and analysis, revise, and hone project--Spring, 2016
- Phase III: Comparative Evaluation/Decision Making--Spring to summer, 2016
  - Approval from the healthcare organization IRB--August, 2016 (see Appendix A)
  - Approval from the University of Northern Colorado IRB--September 2016 (see Appendix B)
  - Proceed with the Delphi survey of SMEs--September to October, 2016
  - Written DNP project completed and submitted—October, 2016
  - Oral Defense of Capstone--October, 2016
- Phase IV: Translation/Application: Plan for implementation of guideline—winter to spring, 2017
- Phase V: Evaluation of guideline through pilot project--Spring, 2017

Resources

Personnel

The work of this capstone was done by the author with assistance from the research advisor and capstone committee members. Members of the Breast Cancer Screening Work Group (BCSWG) within the Organization are working to improve identification of women at high risk of breast cancer and to utilize the latest evidence–based surveillance techniques with this population. This was separate from the capstone. The author of this capstone engaged with this Work Group in the capacity as a doctoral student and healthcare provider in the Organization. The interdisciplinary Work Group synthesized subject matter expertise from medical imaging, primary care, women's health, oncology, surgery, and population and prevention. Some members of this interdisciplinary work group participated in the Delphi survey. A research pharmacist was utilized for baseline data.

Technology

Informatics and Complete Health Solutions (2016) for the Organization were utilized for aggregate member information. The informatics group is formulating a risk assessment mechanism within the electronic health record (EHR) to obtain risk for members. Similar to the BCRAT (modified Gail risk; NCI, 1999), a calculation was generated based on member factors that indicated if a woman was high risk based on a probabilistic estimate (this risk assessment is still in the planning phases of the Work Group). The Delphi survey was distributed through Survey Monkey™ on the Organization's intranet. Descriptive statistics were processed by the Survey Monkey

software and the author with guidance from her research advisor who has expertise in quantitative and qualitative analysis.

Budget

No funding was required specific to this quality improvement project. Work was done on the author's and committee member's time.

Market Analysis, Strategic Analysis, and Service

Justification of Need

The Organization and, specifically, the BCSWG have acknowledged gaps in identifying women at high risk of breast cancer and offering risk reduction therapies, which has led to the development of this DNP capstone project. The most effective breast cancer screening is risk-based and not simply population-based (Amir et al., 2010; Evans & Howell, 2015). Women identified as moderate to high risk need to be informed of their options including lifestyle changes, intensive surveillance, genetic counseling and testing, medications for risk reduction, and surgical prophylaxis as appropriate.

Women want to know their risk of breast cancer (Amir et al., 2010). Currently the Organization is falling behind on the clinical practice guideline and not routinely assessing family history or personal history of radiation therapy for Hodgkin's lymphoma as risk factors. Lack of consistent risk assessment means some women fail to have earlier breast imaging and are not offered risk reduction modalities or intensive surveillance.

The cost of treating breast cancer is considerable for the woman and her family and for health services and public health (Evans & Howell, 2015). This quality improvement project could contribute to cost efficiency over time through learning how to counsel high-risk women regarding chemoprevention for breast cancer within the

healthcare system. Howell and colleagues (2014) asserted implementation of risk screening and chemoprevention would over the long term reduce breast cancer diagnosis.

Feasibility

The Delphi survey was a feasible method to gather opinions from healthcare experts involved in care of women. As the BCSWG takes steps to close gaps in care for women identified as high risk for breast cancer, implementation of risk reduction strategies was a logical next step after risk identification.

Sustainability

With the development of an easy-to-use electronic risk assessment in radiology and in primary care, routine screening for breast (and ovarian) cancer will become the standard of care. Phillips and colleagues (2016) interviewed primary care providers in Australia about parallels in screening for breast cancer as screening was done for cardiovascular health. Themes included the desire for an easy to use endorsed risk tool (Phillips et al., 2016).

Summary

A review of baseline data in the Organization revealed female members were at high risk for breast cancer. These women and their healthcare providers were unaware of the health risks. The evidence indicated women at high risk were not routinely and consistently offered effective medications that could lower their risk. A Delphi method was used to query subject matter experts in the MCO about how to address this gap in care. The responses contributed to the formation of a clinical practice guideline.

CHAPTER III

EVALUATION PLAN

The purpose of this DNP capstone project was to determine how to implement the 2013 U.S Preventive Services Task Force *Breast Cancer: Medications for Risk Reduction* Grade B evidence recommendation to offer pharmacologic agents to women at high risk of developing primary breast cancer at an integrated managed care organization. No current evidence-based recommendation is available within the Organization (Kaiser Permanente, 2016) to guide healthcare providers to discuss and prescribe risk-reducing medications for primary breast cancer for women at high risk. There was ample evidence in the literature that women at high risk of incident breast cancer should be offered SERMS or AIs to reduce risk. Additional evidence was obtained from SMEs utilizing the Delphi method. The author designed a quality improvement project to implement pharmacologic risk-reduction interventions for women at high risk of breast cancer. Each of the three objectives to fulfill this purpose describes evidence–based measures and the method of analysis used.

Objective One

Objective one was to obtain baseline information on chemoprevention use for women at high risk of primary breast cancer at a managed care organization. Two approaches gleaned this information. An analysis of prescriptions specific to tamoxifen, raloxifene, exemestane and anastrozole for women without active or prior breast cancer

was done. The Delphi survey was used to query subject matter experts about their familiarity with chemoprevention recommendations. The measure was the baseline use of chemoprevention. Outcomes would be understanding the current state and its significance to the population. Tools that gathered this data were informatics in pharmacy and Delphi survey rounds. Descriptive statistics were the method of analysis of current state information.

Objective Two

The second objective of the capstone was to evaluate the most current evidence available and the USPSTF's (2013) *Breast Cancer: Medications s for Risk Reduction* recommendation and its applicability to our population. The literature was reviewed for high quality evidence, primarily Level I--Systematic reviews and meta-analysis and Level II--randomized controlled trials, regarding the use of chemoprophylaxis for women at high risk of primary breast cancer (Melnyk & Fineout-Overholt, 2015). Subject matter experts from various disciplines that care for women were surveyed about the applicability of chemoprevention for high-risk women at the Organization (Kaiser Permanente, 2016). As an additional measure, the author compared the literature support for the USPSTF recommendation to the population by means of SME responses to the Delphi surveys. The outcome of objective two was a synthesis of the evidence within the Organization and current literature relevant to medications for risk reduction.

The Rapid Critical Appraisal (RCA; Melnyk & Fineout-Overholt, 2015) checklist for a randomized control trial was the method for analyzing studies' validity, effect size, level of significance, and applicability (p. 546). For systematic reviews of clinical

interventions or treatments, Melnyk and Fineout–Overholt's (2015) RCA tool was used (p. 547).

Objective Three

Objective three of this capstone object was planning for implementation of the USPSTF (2013) recommendation as a clinical practice guideline for providers in the Organization and evaluation of the guideline through a pilot study (the pilot study was not part of this capstone project). Tools to meet this objective were responses from the Delphi survey through Survey Monkey.™ Development of a preliminary guideline was the outcome for objective three. Information from the Delphi survey rounds built consensus toward a guideline. Analyses of survey responses using descriptive statistics formed the method for this objective. The measures resulted in quantitative and qualitative findings.

Summary

The outcome of this capstone project was the understanding of the current state of chemoprevention for high-risk women in the Organization (Kaiser Permanente, 2016), an assessment of the evidence and its applicability to the population, and the development of a clinical practice guideline for pharmacologic risk reduction.

CHAPTER IV

RESULTS AND OUTCOMES

The problem statement for this DNP capstone project was women of increased risk for breast cancer by virtue of concerning family histories, genetic mutations, or personal biopsies were not routinely and consistently offered preventive therapy despite evidence that effective medications could reduce the risk of primary breast cancer (Amir et al., 2010; Cuzick et al., 2014; Howell et al., 2014; Vogel, 2015). The first objective of this evidence-based quality improvement project was to obtain baseline data for the health system on chemoprevention used for primary breast cancer risk reduction. The second objective was to evaluate the most current evidence available and the USPSTF (2013) grade B recommendation *Breast Cancer: Medication for Risk Reduction* and the applicability of this guideline to the population. Objective three was to plan for implementation of a clinical practice guideline and evaluate the guideline through a pilot study (the timeline for the pilot study was after the DNP capstone project and was not part of the actual project).

Objective One Outcomes

The first objective was met through three processes: data from the integrated health systems research pharmacist, information supplied by Complete Health Solutions, and the author's convenience sample survey of 200 women. It was discovered the overall number of prescriptions for tamoxifen, raloxifene, exemestane, and anastrozole for

primary prevention was low--less than 50 for a population of 154,541 women of whom up to 20% could have risk factors that qualified as high risk (Owens, Gallagher, Kincheloe, & Ruetten, 2011; Shah et al., 2012; Traxler et al., 2014). If conservatively 10% of the population was truly high risk of breast cancer, 15,453 women would potentially be eligible for risk reduction strategies; for some, this would include medications. This prescribing information was evidence that use of medication to reduce the risk for primary breast cancer was infrequently used at the health system. The low use of medication has been cited as a common problem in the literature (Vogel, 2010, 2015; Waters et al., 2010). Low primary prevention with medication provides an opportunity for improvement.

The number of women ages 40 to 74 in the health system is 154,541 (A. Bayer, personal communication, July 15, 2016). This information was supplied by Complete Health Solutions (formerly Population Health and Prevention). This was the primary cohort of women affected by this project; however, the author and the Breast Cancer Screening Work Group acknowledged the importance of identifying younger women who might have personal or family factors that made them high risk. The breast cancer high risk registry of the Organization has 364 women known to be BRCA 1 or BRCA 2 gene mutation positive; a population estimate suggested there could be up to 1,800 women with at-risk genetic mutations in the Organization (G. Merry, personal communication, June 1, 2016). The health effectiveness data and information set (HEDIS) metric for the Organization was 76.8% of women 50 to 74 years of age who had screening mammography during 2015 in compliance with USPSTF recommendations for screening (A. Bayer, personal communication, June 17, 2016). According to the Centers for

Disease Control and Prevention's 2015 National Health Interview Survey data, 72.6% of women 50 to 74 years of age reported a mammogram within the two-year screening interval in 2013 (Sabatino, White, Thompson, & Klabunde, 2015). Kaiser Permanente Colorado mammography screening rates are consistent with this finding.

The author's pilot survey was valuable to gain an estimate of the number of women who might be at high risk and thus eligible for genetic referral and/ or consideration of risk-reducing medications. The convenience sample survey used a 2013 clinical practice guideline (Williams, 2013) at the single Ob/Gyn practice to assess for personal and familial risk factors. The findings suggested 25.5% of the population (51/200) had at least one risk factor for primary breast cancer requiring further evaluation. Other valuable aspects of the office pilot survey included an appreciation for the time required for the reviewer (the author) to confirm risk assessment with members' EHR documentation, follow up directly with members by e-mail or phone to clarify responses to the paper survey, provide education to members, determine which members needed referrals to genetics and enter those referrals, assess if medical information and family history was evident in the EHR, and update documentation when needed. Similar to other health networks, the sample of women at the Organization had a subset of women who required further evaluation to determine if they were truly high risk and would benefit from additional surveillance, genetics testing, chemoprevention, or surgical risk reduction.

Objective Two Outcomes

The second objective was a review of the current literature and the 2013 USPSTF guideline to recommend and offer risk reducing medication for women at high risk of

primary breast cancer. The literature review and synthesis in Chapters I and II met this objective. Nelson et al.'s (2013) systematic review for the USPSTF presented evidence for the recommendation including the following formative studies: The Breast Cancer Prevention Trial (Cuzick et al., 2003; Fisher et al., 1998), STAR (Vogel et al., 2010), MAP.3 (Goss et al., 2011), and the Multiple Outcomes of Raloxifene Evaluation (MORE; Cauley et al., 2001).

The Delphi study of chemoprevention for primary breast cancer was developed to learn subject matter experts' opinions on the use of the USPSTF (2013) recommendation for risk reducing medications.

Surveys

The author developed the first and second survey questions based on evidence in the literature and knowledge of the population and health system. The purpose of the Delphi surveys was to gather information from subject matter experts regarding the USPSTF (2013) grade B recommendation for providers to discuss and offer risk-reducing medication to women at high risk for primary breast cancer and to use these findings to develop a clinical practice guideline for the Organization. Consent for participation was provided with the first survey and implied panelist response (see Appendix D). The first survey was available for 14 days. Questions are available in Appendix E. The second survey was designed to build toward consensus and was available for 14 days. Questions are available in Appendix F. All panel experts included in round one were invited to respond to round two regardless of their participation in the first round.

Participants

For this DNP capstone project, a panel of subject matter experts in women's health from the disciplines of family medicine, internal medicine, Ob/Gyn, surgery, pharmacy, nursing, oncology, radiology, and administration were queried on the option to discuss and offer risk-reducing medication at the Organization. Forty-nine health professionals from nine disciplines were invited to participate in the survey through the in-house online intranet. Physicians, nurse practitioners, and physician assistants in the various disciplines were invited as were pharmacists, registered nurses in oncology, and care coordination in radiology and surgery. Administrators in population health management, Ob/Gyn, and nursing were invited to the subject matter expert panel. As the Organization covered a metropolitan region, panelists were chosen from the three administrative regions: the north (15 providers), the central (18 providers), and the south (13 providers). The first round Delphi survey generated a 30.6 % response rate with 15 respondents. Fourteen of the 49 responded to round two for a 28.5% response. Seven of the nine disciplines were represented in the first survey. Registered nurses might have identified with their specialty department, such as radiology, rather than nursing as their primary discipline (see Table 2). Two survey rounds were needed to obtain the information. Physicians and advanced practice nurses were equally represented among panelists with each group representing 40% of panelists (6/15 each group). One each--physician assistant, registered nurse, and administrator--comprised the rest of the subject matter experts consulted.

Table 2

Demographics of Subject Matter Experts in Delphi Survey

Discipline	Number Invited to Participate	Number of Participants	Percentage Overall	Total Participants
Family Medicine	8	4	26.7	4
Internal Medicine	6	0	0.0	4
Nursing (RN)	4	0	0.0	4
Ob/Gyn	8	5	33.3	9
Oncology	12	1	6.7	10
Pharmacology	3	0	0.0	10
Radiology/Medical imaging	6	2	13.3	12
Surgery	4	1	6.7	13
Administration	3	2	13.3	15

By round two, there was 100% agreement that the 2013 USPSTF recommendation to discuss and offer SERMs and aromatase inhibitors was a reasonable course of care, suggesting providers could feel comfortable following this recommendation (Question 2, see Appendix F). The author details how that consensus emerged.

Data Collection Description

Data were collected between September and October of 2016 using the SurveyMonkey online platform program. Questions were intended to glean opinions regarding the USPSTF (2013) recommendation as well as items necessary to develop a clinical practice guideline to enact the recommendation. Rounds one and two of the

Delphi surveys were sent through the Organization's intranet. The majority of panelists responded within the first three days of the survey's release: 46.7% (7/15) for round one and 71.4% (10/14) for round two. Consensus was reached in round two for the majority of questions (5/7 questions; see Appendix F). Consensus for this project was defined as .70 or above agreement among the responding panelists.

Objective Three Outcomes

Evidence gathered for the planning of a clinical practice guideline within the Organization and testing the guideline through a pilot study comprised the third project objective. An analysis of responses to round one questions helped form the second round. The questions were structured to assess knowledge about medication use for primary breast cancer risk reduction and elicit opinions to guide the development of a clinical practice guideline.

Round One Delphi Survey

In round one, question four, 71.4% of panelists (10/14) believed the Organization was not reaching women at high risk for breast cancer with information to help reduce their risk. Comments to this question included:

- This is the first that I have even heard of doing this.
- Besides reminders for yearly mammograms there does not seem to be an advertising campaign or push through text or email to notify women.
- Not sure. I rec mammos but that is it.
- I ask all my patients about family history of breast cancer.
- I don't believe time allows for conversations to occur to reduce the risks. However, I believe we are discussing mammogram and ultrasound/MRI recommendations.
- I am not sure what we are doing.

- I have had very few conversations with women about their actual numeric risk and I have never prescribed prophylactic treatment
- I do not see this flagged on the Health Trac tab [Health Trac is a population health prevention reminder tab for all healthcare providers].

The limited use of risk-reducing medications for women at high risk of primary breast cancer and evidence from the literature supported the development of a clinical practice guideline. Eighty percent of the panelists (12/15) did not know if medications for primary breast cancer risk reduction were being offered or provided at the Organization. Of the three panelists who indicated medications were being offered to reduce risk, one panelist was an oncologist, one was a breast surgeon, and the third was an administrator in the Ob/Gyn department. The surgeon and oncologist added comments that oncology should be the service counseling and prescribing SERMs and aromatase inhibitors for appropriate high-risk women.

A follow-up question asked about current use of SERMs or aromatase inhibitors for high-risk women. Nearly 80% (78.6%, 11/14) indicated the medications were offered by providers in other departments while 14.3% (2/14) indicated an understanding that providers in their department--Ob/Gyn and oncology—offered the medication. Of the 12 panelists who responded to question 7--"If risk reducing medications are currently discussed and prescribed, which discipline is doing this? (Can choose more than one answer)," 83.3% (10/12) indicated oncology while 25% (3/12) also indicated Ob/Gyn providers. Asked whether risk reducing medications should or should not be recommended, 28.6% (4/14) indicated medications should be recommended more frequently than are currently done and none of the panelists indicated medications should not be recommended (see Appendix F). One oncologist panelist (6.7%) expressed the

current process of offering and prescribing SERM and AIs to high-risk women was working adequately. One Ob/Gyn advanced practice nurse (6.7%) indicated the current process was working poorly and the remainder 86.7% (13/15) did not know how well the current process of offering risk reducing medication to high risk women was working in the Organization.

A survey item inquiring what facilitated or hindered counseling women about medications for primary breast cancer risk reduction generated eight qualitative responses that fell into four categories**:**

1. High risk of breast cancer not identified
    - High risk women are not uniformly identified in our Organization.
    - Family hx is not adequately documented in chart. Do not see as a dx on the problem list.
2. Time for counseling and education of member
    - Time spent by provider, lack of knowledge.
    - Time and lack of provider knowledge (lack of personal knowledge/ information).
3. Healthcare providers lack of knowledge
    - Not being knowledgeable about the medications hinders counseling.
    - I need more education on when to provide prophylactic therapy both pros and cons.
    - Proper guideline recommendations/cost of medicine.
4. Other
    - Lost to care, as many people are in and out of different insurance providers often.

These comments were valuable for developing a guideline (see Appendix G). In order to offer a medication to high-risk women, those women must be identified. The Organization is in process of acquiring and implementing a software package in medical imaging that will solicit risk factors from women at the time of mammography. These risk factors calculate a breast cancer risk score for individual woman using the BRCAPRO tool (Bayes Mendel lab, 2015; CRA Health, 2016). This information is currently gathered on paper and scanned to the radiology information system (RIS) but not linked electronically to the EHR providers can access. The Breast Cancer Screening Work Group, of which the author is a member, is working with Complete Health Solutions (2016) and information technology to develop a mechanism to quickly identify high-risk women who are not evaluated in medical imaging. We anticipate a process in place by winter-spring 2017 as the radiology software system will be implemented at that time.

Time for risk assessment, education, and shared decision making with female members is a legitimate challenge in busy clinic settings. The Organization has information on the Kaiser Permanente member portal to assist women in their decision to have a mammogram as well as decision points for women at high risk (Kaiser Permanente Healthwise, 2015). Traxler and colleagues (2014) implemented a breast cancer risk assessment tool in public health clinics that added five minutes to the encounter. Time concerns were addressed by providing the woman information to review and then having a follow-up phone call or in-clinic encounter for further discussion.

The need for clinician education was addressed by various mechanisms. In round two, panelists indicated a departmental in-service was their preference (76.9%, 10/13) as the most effective way to gain this knowledge. One panelist commented that in addition to continuing medical education through a departmental in-service, having office champions to guide the process, Smart Rx for prescribing in the EHR, information on the clinical library, and an advice referral to a specialty would optimize the knowledge gain needed on this issue. Another panelist indicated having a high-risk breast clinic would be preferred.

The comment about members lost to care as a hindrance to counseling could be partially addressed by informing the member of her breast cancer risk status. Adding high risk for breast cancer to the problem list using ICD-10 (ICD10Data.com, 2016) code Z80.3, family history of breast cancer, or whatever diagnosis was appropriate would alert other care providers to her status at future encounters. The diagnostic codes are listed on the clinical practice guideline to facilitate documentation for providers (see Table 1 in Chapter II).

The final survey questions in round one (questions 11 and 12) asked panelists for their opinion regarding the 2013 USPSTF recommendation that clinicians engage in shared informed decision-making with women at increased risk for breast cancer about medication to reduce their risk and how they envisioned implementation of the recommendation at Kaiser Permanente Colorado. Responses included a range of comments organized into the following themes: (a) a multidisciplinary team for guidance; (b) primary care and Ob/Gyn providers identifying and providing medications to appropriate high risk women members; and (c) an infrastructure to support the change.

Multidisciplinary team. Panelists commented that oncology, adult genetics, and clinical pharmacy would serve as consultants to primary care and Ob/Gyn clinicians regarding chemoprophylaxis. An individual panelist stated, "Identify high risk woman by primary care, confirm by genetics, and refer to oncology or OBGYN for counseling medication needs." Others wrote about envisioning: "Use a multidisciplinary team working together" and "Identifying those high risk women [in primary care] and getting them to oncology department."

Primary care and Ob/Gyn role. A panelist provided a specific comment: "Primary care, Ob/Gyn and surgery should have adequate information to counsel patients and their families about management/medication option." Five panelists (33.3%) wrote similar comments that primary care and Ob/Gyn providers could identify women at high risk and "provide this care." The USPSTF (2013) recommendation specifically stated,

> clinicians engage in shared informed decision making with women who are increased risk for breast cancer about medication to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk- reducing medications, such as tamoxifen or raloxifene. (Recommendations, para. 1)

One panelist felt specialists and not primary care were best suited to address risk-reducing medications. One wrote,

> Refer to a trained or educated professional who knows breast cancer and preventative medications, breast specialist or oncologist, possibly trained GYN providers who have obtained additional education about these medications, who is (sic) appropriate candidates.

Infrastructure. One panelist wrote what was needed was a "formalized process in targeted departments that discuss the same information and document the same." Another panelist provided a comprehensive view:

> We need both proactive and in-reach efforts. An infrastructure should be built to identify those at high risk who should be offered therapy. The process can be put in place to proactively outreach these members and have an alert on the Health TRAC tab about this high risk and to consider prophylaxis. Improved education [is needed]. Need funding to set this. A multidisciplinary team would need to be assembled to address this. I believe some of this is underway. I think this care can be provided in OB/Gyn and primary care and oncology could be used as a consultative service.

An additional comment from a family medicine advanced practice nurse addressed the need for an infrastructure with this comment; use of this recommendation

> could be done along the lines of CAD risk prevention and outreach with use a tool like IndiGo. With clear clinical guidelines and recommendations. Primary care could [offer & prescribe] along with support from clinical pharmacy and oncology.

IndiGo is a population health clinical decision support tool for use at the point of care with patients (Doherty, 2016). IndiGo was developed for the purpose of bringing evidence based practice into care.

One panelist wrote that members lack education around risk stratification and mechanisms to reduce risk. An outreach effort such as a "know your breast cancer risk campaign" could be launched within the Organization to encourage members to seek out their personalized breast cancer risk much like cardio-vascular risks.

An oncologist from on the panel wrote a noteworthy comment:

> KP participated in the original NSABP trials for tamoxifen in prevention 20+ years ago; the long term follow up of these studies does not show an improvement in overall survival. Most docs and patients don't know the actual facts of this trial that one needs to treat 65 women to prevent one breast cancer. Nationwide I think the enthusiasm initially present to use these drugs has decreased. I think it is acceptable to use in women who express interest, but I don't think it is justified or necessary to actively recruit more women for prevention.

Despite the evidence indicating a reduced risk of breast cancer in high-risk women through chemoprophylaxis, these medications did not produce a decrease in breast cancer

mortality among women at high risk. Some plausible explanations for this are SERMS reduce the rate of estrogen receptor-positive breast cancer but not hormone receptor-negative breast cancers (Fisher et al., 2005). With regard to recruiting women, the author felt strongly women need to know their personal health risk as much as possible so if they choose to gain additional information from clinical experts to make informed choices. These points from panelists are incorporated into the clinical practice guidelines (see Appendix G).

Round Two Delphi Survey

The Delphi survey rounds were illustrative: nearly 70% of respondents (69.2%, 9/13) agreed that having a prompt in the EHR to screen women for high risk status was something they would use. Some panelists worked in specialty disciplines such as oncology, surgery, and radiology and the member's risk status was determined prior to the member's encounter in their specialty department. One panelist who disagreed recommended they would "rather see a prompt to complete family history, then if that is positive, a prompt to do proper screening and treatment." In the author's pilot survey in an Ob/Gyn practice, family history of breast and ovarian cancer was correctly noted in the chart 87.4% of the time (49/56). In the problem list of the EHR, 33.9% of those with risk factors (19/56) had some documentation of high risk for breast cancer such as family history. The problem list was a more prominent location of important health issues for all health providers as documenting pertinent family history is critical to identifying women at high risk.

In response to the question--"Would you agree that having a prompt in Health Trac that screens for high risk status is something you would use?", four panelists

answered they would not use a prompt in the EHR that screened for high-risk status. Two of them left the following comments: “If there were specific recommendations to follow” and “Unsure. It depends on what the prompt requires.”

Specific recommendations were addressed in the clinical practice guideline. The prompt included information from the current Kaiser Permanente Colorado 2013 Clinical Practice Guideline (Williams, 2013) about personal history of breast cancer or abnormal biopsy, first degree relative with breast cancer and age of diagnosis, family or personal history of *BRCA1* or *BRCA2* mutations, and radiation treatment to the chest.

All respondents of round two agreed following the USPSTF (2013) recommendation to discuss and offer SERMs and aromatase inhibitors for selected high risk women was a reasonable course of care. The USPSTF recommendation formed the foundation of the clinical practice guideline. Eighty-three percent (10/12) agreed primary care and Ob/Gyn providers with appropriate training could and should initiate the discussion about chemoprevention with high-risk women. One who indicated they would not support primary care and Ob/Gyn initiating these discussions with high-risk women commented, “It seems like too nuanced a discussion to add to the PCP plate.” The guideline addressed the nuances of the discussion.

For the development of a guideline, panelists were asked,

> Many respondents suggested having specific guidelines for discussions with members about SERMs and AIs for risk reduction. A clinical practice guideline would
> 1. Indicate the mechanism for identifying women at high risk, and when that risk status will be reassessed;
> 2. Inclusion / exclusion criteria;
> 3. the medication appropriate for the woman based on her menopausal and health risk status, dosage, and risks/benefits, length of time of medication use, and management of side effects.
> 4. and alternatives to the medication

> Do you agree this forms the basis of a guideline? If no, what needs to be included?

There was 92.9% agreement that this information formed the basis of a guideline. One panelist (7.1%) disagreed and commented, "A discussion that includes number needed to treat to prevent one breast cancer which is 65 and the fact that there is not a survival improvement with these medications." It is true--the evidence showed no improvement in breast cancer deaths with SERMs or AIs; providers and members must be informed of that. Based on randomized control trials, the number needed to treat (NNT) with tamoxifen daily for greater than five years to prevent one breast cancer was 48 women, the NNT for raloxifene for four years was 112-115 women, the NNT for exemestane over three years was 94 women and 26 women in five years, and the NNT for anastrozole in seven years was 36 women (Advani & Morena Aspitia, 2014, pp. 67-68). For comparison, the NNT for primary prevention of myocardial infarction with statins is 60, which is a widely adopted population health strategy (Taylor et al., 2013). Women need to be aware of these risk and benefits to make an informed decision. These recommendations from panelists have been included in the guideline (see Appendix G).

In round two, question 7 did not reach a consensus of opinion among panelists: **"**For planning purposes, if support is needed for these discussions with members, or the woman desires a second opinion, who would we refer to?" Forty-six percent of respondents (6/13) selected oncology as the consultant discipline, pharmacy was the choice for 23% of respondents (3/13), 15.4% selected Ob/Gyn (2/13), and 15.4% selected genetics (2/13). One of the 14 respondents commented they "were not sure [how to answer] since oncology would ideally be the first opinion." That panelist did not select a consultant discipline. If that answer had been added to the group that selected oncology,

53.8% (7/13) would have chosen oncology as the discipline for consultations about risk-reducing medication for primary breast cancer. The range of responses reflected no discipline had owned chemoprevention, thus supporting the need for a guideline.

In planning the implementation of the clinical practice guideline, the author discussed with oncologists and pharmacists regarding their comfort and willingness to consult on these high-risk members. At the quarterly meeting of the Breast Cancer Leadership on June 1, 2016, an opinion expressed by oncologists was they would like to have a consultation appointment if women were interested in chemoprevention (G. Merry, personal communication, June 1, 2016).

Key Facilitators and Key Barriers to Project Objectives

Facilitators

Factors that facilitated the collection of information on chemoprevention within the health system were (a) metrics kept through an accessible pharmacy data warehouse, (b) the in-house communication intranet for the Delphi survey, (c) women members' willingness to complete a short six question breast cancer risk assessment survey in the Ob/Gyn department, and (d) the ease of developing an electronic survey through the Survey Monkey platform. The author believed interest in this topic from providers in several disciplines was instrumental in generating a response. It may have helped that the Breast Cancer Screening Work Group of the Women's Health Governance Council has been focused on addressing breast cancer risk stratification within Kaiser Permanente Colorado (2015) over the same time of this DNP project (past year). At least one health provider mentioned in the comments to the first round survey, "I believe some of this

[work] is underway" utilizing a multidisciplinary team to identify high risk members. The multidisciplinary team is the Breast Cancer Screening Work Group.

The author's active participation on the Breast Cancer Screening Work Group (Work Group) might have been both a facilitator and a barrier to this DNP project. The group has members from Ob/Gyn, radiology, population and prevention, oncology, internal medicine, and surgery. Benefits from the Work Group included contacts with clinicians and administrators passionate in improving the quality of breast cancer screening in the Organization. Access to genetic counseling specialists in partnering regions, particularly California, was helpful in the early phases of the project. A barrier was the Work Group's primary focus on identifying high-risk women evaluated in the radiology department. At times, the author was pulled off track from this project by providing literature reviews for the Work Group on breast cancer risk assessment tools and strategies for care of women at moderate risk of breast cancer. Overall, the experience with the Work Group has been positive and allowed for partnership in the development of this project.

Barriers

Multiple competing demands for healthcare provider's time are often expressed as a reason for limited participation in surveys. Higher participation from oncology, pharmacy, and internal medicine would have added a more comprehensive view to responses to the Delphi surveys. The author could have opted to invite more participants into the study. The selection of participants was subject to bias and was not randomized. The author selected some participants from the Breast Cancer Screening Work Group as the topic was important to these providers. One region's oncology providers and

internists were selected by asking the author's colleagues who would be most interested in this topic. The author also selected participants whom she felt would be more likely to respond.

Obtaining the number of prescriptions for medication used as primary breast cancer chemoprevention was a challenge. Understanding how to ask the question in the right way to get the information needed from those who have access to the data warehouse was crucial. Experience from the final project in the Information Technology in Health course of the DNP program provided a baseline understanding of the required linking of clinical diagnoses with a prescription to obtain the desired results. The author discovered if a prescription was not linked to an ICD-10 (ICD10Data.com, 2016) diagnostic code, it was not possible to track or retrieve that prescription. A limitation of this project was the retrieval process might have underestimated the number of written orders for SERMS or aromatase inhibitors for primary breast cancer risk reduction.

Unintended Consequences

An unintended consequence of this project included the author's recognition of the complexity of chemoprophylaxis counseling. Newly armed with empirical data and practical recommendations for discussion of risks and benefits with high-risk women, the author fumbled through the information she needed to convey during a scheduled patient appointment. The identical twin sister of the patient was diagnosed with infiltrating ductal carcinoma of the breast six months earlier at age 48. The patient wanted to know what steps she should take to confront this risk. This woman was in general good health, was still menstruating, and took no medications. She was scheduled every six months for breast imaging, alternating mammogram with breast MRI. Her Gail (Gail et al., 1999)

five-year risk score was 1.8% and her lifetime breast cancer risk score was 17.3%. Thus, her five-year risk met the high-risk criteria but not the 3% risk recommended by the 2013 USPSTF recommendation to begin risk-reducing medication. Her lifetime risk fell in the moderate category (20% or greater is high risk). This education and counseling did take time. While developing the guideline, it became clear talking points to guide providers were helpful. Teaching tools for members would also facilitate education and outreach.

A negative unintended consequence of this project was the time it took the author to settle on the appropriate DNP project topic among breast cancer concerns. This has been a meandering journey. An initial topic was breast density detected on medical imaging as that is a risk factor for breast cancer. While many states have breast density notification laws, Colorado does not. While discussing this with the mammography quality and safety manager, she mentioned an issue within Kaiser Permanente Colorado was creating and maintaining a registry for women at high risk for breast cancer. At that point, the author became involved with the Breast Cancer Screening Work Group of the Women's Health Governance Council. The Work Group was creating a means to risk-stratify women. Breast cancer risks are heterogeneously dispersed among women. Within the Work Group, focus has been on the unaffected--women who do not have breast cancer but are at higher risk based on familial or personal risk factors. A goal has been to identify these women and, through this project, be aware of strategies to lower the risk for selected women.

The author became interested in risk-reduction medications while reviewing the literature for the Work Group regarding risk screening tools. Chemoprophylaxis is an area of primary prevention in which advanced practice nurses can take an active role.

Discussion with the DNP project committee helped solidify that chemoprophylaxis of primary breast cancer for women at high risk was a project with sufficient complexity to meet the aims of a DNP capstone while also meeting the needs of the Organization. Individualized breast cancer risk assessment is an important topic for the Organization and steps are being undertaken to provide this through the use of an electronic questionnaire at the time of mammography. This tool, called MagView, stratifies women into high (greater than 20% lifetime risk), moderate (15-19.9% life time risk), and average risk pools. It is expected to be available in the first quarter of 2017. High-risk women will be asked to consult with their healthcare providers (see Appendix G algorithm) for the next steps in care. It is anticipated the contributions of this DNP project will be useful for providers and members learning of high risk status.

Summary

Baseline information on current use of chemoprevention for women at high risk of breast cancer has been obtained (objective one). The most current evidence for risk reducing medication and the USPSTF (2013) *Breast Cancer: Medications for Risk Reduction* recommendation and its applicability to the Organization's population was evaluated; it was found to be relevant and of good quality. The planning for implementation of the recommendation as a clinical practice guideline is underway. The Delphi survey obtained valuable and pertinent opinions on willingness of providers to offer and prescribe SERMS and aromatase inhibitors for women at high risk of breast cancer and how specialists, particularly in oncology, could be used for consultation.

CHAPTER V

RECOMMENDATIONS AND IMPLICATIONS FOR PRACTICE

The problem statement for this DNP project was women at increased risk of primary breast cancer due to personal or family histories, genetic mutation, or mantle field radiation at a young age had not routinely and consistently been offered preventive therapy despite evidence such therapy could reduce breast cancer from 25% to nearly 50% (Amir et al., 2010; Cuzick et al., 2014, Howell et al., 2014; Vogel, 2015). Implications for the Organization are risk assessment for primary breast cancer could be routinely and consistently done. This information would allow for the identification of high-risk women who can benefit from primary prevention of breast cancer. Many clinicians, including the subject matter expert panel and this author, acknowledged the 2013 Grade B recommendation from the USPSTF to discuss and offer SERMs and aromatase inhibitors to high risk women was a reasonable course of care. Leadership within the Organization supported providers' steps to improve breast cancer risk assessment to identify high risk women and offer appropriate evidence-based surveillance and prevention strategies as evidenced by the purchase of a new software package in radiology, the formation of the Breast Cancer Division, the Breast Cancer Screening Work Group, and this DNP project. The recommendation from the DNP project was to

use breast cancer risk status to offer risk reducing medication as appropriate. The clinical practice guideline will facilitate processes for the clinician (see Appendix G).

Key stakeholders included adult female members, particularly those with family history of breast and/or ovarian cancer or prior breast biopsies indicating atypical hyperplasia or Lobular Carcinoma in Situ or women who had mantle field irradiation to the chest. New members to the Organization as well as existing members would benefit from a risk assessment and clear documentation in the EHR. Additional stakeholders are primary care providers including advanced practice nurses and physician assistants in family medicine, internal medicine, and Ob/Gyn. The clinical practice guideline facilitates care for women determined to be at high risk. It is envisioned that specialists in genetics, surgery, oncology, and pharmacology would serve as consultants to primary providers. An oncologist was the lone negative response to the Delphi survey question that primary care and OB/Gyn could and should initiate discussions about chemoprevention with high-risk women. The oncologist expressed, It seems like too nuanced a discussion to add to the primary care providers' plate," implying education and orders should only be done by oncology. It would be wise for the author to meet with interested oncologists to clarify if the views expressed in the Delphi survey represented the discipline. Do oncologists view their role as consultants for chemoprevention or the primary providers of these medications to at-risk women?

For the DNP student author, it was clear a Delphi process was an efficient way to gather views from various disciplines without the challenge of getting multiple providers in a single setting. This iterative process allowed for many voices on the topic (Keeney, Hasson, & McKenna, 2006). A limitation of the Delphi survey method was potential

panelists could decline to participate as 70% of invitees did for this project. The Delphi survey of nine different disciplines allowed for many opinions to contribute to a practice change. A limitation of the Delphi was bias could occur toward the opinions of those who replied.

Clinical practice guidelines are based on scientific evidence but might not accommodate members or work environments. The next step for implementation is to pilot the guideline.

Recommendations Related to Facilitators, Barriers, and Unintended Consequences

As many of round one respondents indicated they needed more information about benefits and risks to counsel women effectively, a round two question inquired what respondents felt would be the best way to obtain this information. The majority (76.92%, 10/13) selected a departmental in-service as their way to learn with a specific comment from one panelist that an "adult primary care continuing medical education session" would be preferred. A webinar was selected by 15.38% of respondents (2/13) and 7.69% (1/13) selected office champions to teach this information. Another panelist added a comment that in addition to a departmental in-service would be office champions knowledgeable about the "Smart Rx" in Health Connect, which is the template in the EHR, and information in the clinical library along with a link for an advice referral to specialty (which specialist was not stated). The Smart Rx would list specific orders for tamoxifen or raloxifene. Those comments helped complete items needed for a guideline. Interestingly, one panelist stated a high-risk breast cancer clinic would be best to meet providers' education needs.

Ongoing Activities or Evaluations Outside the Scope of the Doctor of Nursing Practice Project

The Breast Leadership Council of the Organization (Kaiser Permanente, 2015) is moving toward creation of a Breast Care Division to improve the member's experience of breast cancer care. Leadership has decided not to pursue a Center of Excellence designation at this time due to unique aspects of the Organization's integrated health system (A. Weinfeld, personal communication June 1, 2016). Other changes in progress include the transition to a new software system in medical imaging that plans to obtain risk assessment using the BRCAPRO risk tool (Bayes Mendel Lab, 2016). This DNP project complemented the radiology changes as having a guideline and education sessions to introduce it could potentially ready providers to discuss and be familiar with risk reduction medications.

Recommendations Within the Framework of the Organization's Strategic Plan

Prevention of common health problems, early detection of disease, and risk reduction are hallmarks of the Organization. In order for the membership to "Thrive" (Kaiser Permamente, 2016), which is the Organization's motto, members need to be well informed of their personal health risks and strategies to impact those risks.

A supporting organization for this project was the Women's Health Leadership team and, specifically, the Ob/Gyn Regional Value Advisor and the Department Value Advisors from radiology and women's health, both of which serve on the Breast Cancer Screening Work Group. Radiology has partnered with women's health to plan for changes to breast cancer risk assessment in the Organization. Complete Health Solutions

(Population Health; 2016) has been instrumental in developing strategies for communication with members.

Personal Goals and Contribution to Advanced Practice Nursing

The author's personal goals in advanced practice nursing included the ability to make positive changes in the healthcare environment that promote women's health**.** To demonstrate skills learned in the DNP program including evaluation of empirical evidence was another goal. The author aimed to impact care at a broader population level than the individual patient encounter. The process of this DNP project has given this author experience in many aspects of the course work ranging from epidemiology to information technology to evidence-based practice to the Stetler (2001) framework as a theory. The author also strove to demonstrate talents, skills, and problem solving abilities of advanced practices nurses with the healthcare team.

Essentials of Doctoral Education for Advanced Nursing Practice

The American Association of Colleges of Nursing (AACN) developed the eight essentials for Advanced Nursing Practice in October 2006 (see Appendix H). The goal of the Doctor of Nursing Practice educational program is to develop practice experts (AACN, 2006, p. 7). The author incorporated many of the eight essentials into this DNP project, reflecting learnings over the course of study.

Essential I is scientific underpinnings for practice. The comprehensive and current literature review and analysis met this goal. Organizational and systems leadership for quality improvement and systems thinking is Essential II. This concept maintains an emphasis on practice, ongoing improvement of health outcomes, and

ensuring patient safety (AACN, 2006, p. 10). The development of this DNP project for consideration of chemoprevention and a clinical practice guideline detailing how to implement the practice change conceptualized a new care delivery model based on science and was feasible within the current Organization's political, cultural, and economic climate (ACCN, 2006, p. 10). Planning for change within an organization can be difficult. Partnerships with other passionate clinicians and population health specialist kept the energy sustained.

Clinical scholarship and analytic methods for evidence–based practice is the third Essential (AACN, 2006). As one DNP committee member called it, "intellectual curiosity" has been a trait of this author. This DNP program has helped this author challenge thoughts and energies into a scholarly project and translate the evidence into practice to meet a need in our clinical setting.

Use of information systems and technology and patient care technology for the improvement and transformation of health care, Essential IV (AACN, 2006), was evident in this project through the development of the Delphi surveys on the Survey Monkey platform, the pilot survey at the author's clinic facility, and the need to obtain data on prescription use and numbers of women impacted at the Organization. Existing decision-making electronic tools for members at high risk could be utilized to help the individual woman understand her health values (Kaiser Permanente, 2015; see Appendix G for guideline).

Essential V (AACN, 2006) describes Health Care Policy for Advocacy in Health Care. Several states now have breast density notification laws. Colorado does not but might have such a law in the future. Good quality evidence exists that breast density

increases one's risk for breast cancer (Boyd, 2013). Since there has been no consensus among researchers, clinicians, and cancer organizations on how to follow up on breast density noted on mammography, this was not addressed in the project. New risk models will likely incorporate mammographic breast density as another factor in risk assessment (Boyd, 2013). A discussion with colleagues of how breast density could be addressed in our system in a state that does not yet have a patient notification law began the path to this current DNP project topic. This project did not create or impact healthcare policy.

Interprofessional collaboration for improving patient and population health outcomes, the component of Essential VI (AACN, 2006), was necessary to develop and perform this project. The multidisciplinary team of the Work Group and the panelists contributed to development of the clinical practice guideline. Population health outcomes will be improved through discussions between women and their providers regarding risk status and chemoprophylaxis for primary breast cancer prevention. Essential VII's focus was clinical prevention and population health for improving the nation's health. This project was focused on disease prevention and population health. Advanced nursing practice, Essential VIII, was exemplified in this project as it met Waldrop, Caruso, Fuchs, and Hypes (2014) definition of the final DNP oroject as one "that should address a complex practice, process, or systems problem in the practice setting, (and) use evidence to improve practice process, or outcome" (p. 301).

Five Criteria for Executing a Successful Doctor of Nursing Practice Final Project

Waldrop et al. (2014) described a five-point system of evaluating the final DNP project represented by the formula EC as PIE.

E equals enhances health outcomes, practice outcomes, or healthcare policy (Waldrop et al., 2014, p. 301). The project enhanced practice outcomes through use of evidence to educate and offer a risk-reducing strategy to women at high risk of breast cancer.

C equals culmination of practice inquiry (Waldrop et al., 2014, p. 302). The author has become an expert on chemoprevention for high-risk women and used knowledge and competencies learned in the doctoral program to enact change (Waldrop et al., 2014, p 302). The change is pragmatic and anticipated to be used in clinical practice in a timely, reproducible, and sustainable fashion. The design for the practice change integrates with the EHR as recommended by Waldrop et al. (2014).

P equals partnerships. Partnerships were formed through this project and the author collaborated on an interdisciplinary team within the Organization (Waldrop et al., 2014, p. 302). I equals implement evidence into practice. It is insufficient to simply find and evaluate evidence--it must be applied (Waldrop et al., 2014, p. 302). Implementation of the clinical practice guideline for risk-reducing medication for women at high risk of breast cancer is planned. E equals evaluation of healthcare practice outcomes (Waldrop et al., 2014, p. 302). Quality improvement will be evaluated on the use of the guideline. Criteria for evaluation are (a) does it facilitate education and care, (b) is it easy for clinicians to use, and (c) are more women informed of their breast cancer risk and strategies to lower those risks, (d) are more prescriptions written for primary prevention, and (e) are more referrals made to oncology for members to discuss risks and medication for prevention? These factors and perhaps others will comprise the evaluation of the

practice change. The evaluation process will occur after the submission of the final DNP project.

Summary

The DNP project addressed an aspect of women's breast health that has often been neglected due to the perceived complexity of the issue and difficulty identifying high-risk women. There is good quality evidence, largely from randomized controlled trials, that SERMs and aromatase inhibitors can reduce the risk of estrogen receptor-positive primary breast cancers for high-risk women (Fisher et al., 1998; Goss et al, 2011; Vogel, 2015). The 2013 USPSTF recommended clinicians offer and prescribe SERMs and AIs to women with a five-year Gail (Gail et al., 1999) risk score of 3% or greater or women with a 20% lifetime risk of breast cancer. These medications are not without risk and do not decrease breast cancer mortality. Women who meet criteria need appropriate education and counseling to make informed choices consistent with their lifestyle and values. The clinical practice guideline facilitates care for these women with detailed information for providers and members.

REFERENCES

Advani, P. & Morena-Aspitia, A. (2014). Current strategies for the prevention of breast cancer. *Breast Cancer: Targets and Therapy. 6,* 59-71. doi.10.2147/BCTT.S39114

Agency for Healthcare Research and Quality. (2013). Medication for risk reduction of primary breast cancer. *Annals of Internal Medicine, 159*(10) 698-708.

American Association of Colleges of Nursing. (2006, October). *The essentials of doctoral education for advanced nursing practice.* Retrieved from http://www.aacn.nche.edu/dnp/Essentials.pdf

American Cancer Society. (2016a, August 18). *Breast cancer: What are the risk factors for breast cancer?* Retrieved from http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors

American Cancer Society. (2016b, August 18). *What is breast cancer? Topics: What are the key statistics about breast cancer?* Retrieved from http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics#top

American Society of Clinical Oncology. (2013, July 8). *Use of pharmacologic interventions for breast cancer risk reduction: Clinical guideline*. Retrieved from https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9816

Amir, E., Freedman, O. C., Seruga, B., & Evans, D. G. (2010). Assessing women at high risk of breast cancer: A review of risk assessment models. *Journal of the National Cancer Institute*, *102*(10), 680-691.

Bayes Mendel Lab. (2015). *BRCAPRO breast cancer risk assessment tool*. Retrieved from http://bcb.dfci.harvard.edu/bayesmendel/software.php

Bellcross, C. A, Lemke, A. A., Pape, L. S., Tess, A. L., & Meisner, L. T. (2009). Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. *Genetics in Medicine, 11,* 783-789. doi:10.1097/GIM.0b013e3181b9b04a

Boyd, N. F. (2013). *Mammographic density and risk of breast cancer*. Retrieved from http://meetinglibrary.asco.org/content/227-132

Butow, P., & Phillips, K. A. (2016). Medication to reduce breast cancer risk: Why is uptake low? *Annals of Oncology*, *27*(4), 553-554. doi:10.1093/annonc/mdw043

Cauley, J. A., Norton, L., Lippman, M. E., Eckert, S., Krueger, K., Purdie, D.W., ….Jordan, V. C. (2001). Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: Four-year results from the MORE trial--Multiple outcomes of raloxifene evaluation. *Breast Cancer Research and Treatment, 65*(2),125–134. doi:10.1023/A:1006478317173

Cazzaniga, M., & Bonanni, B. (2012). Breast cancer chemoprevention: Old and new approaches. *Journal of Biomedicine and Biotechnology*, *2012*, 985620. doi.org/10.1155/2012/985620

Colditz, G. A., Wolin, K. Y., & Gehlert, S. (2012). Applying what we know to accelerate cancer prevention. *Science Translational Medicine, 4:*127rv4. doi:10.1126/scitranslmed.3003218

Collins, I. M., Steel, E., Mann, G. B., Emery, J. D. Bickerstaffe, A., Trainer, A., …Keogh, L. (2014). Assessing and managing breast cancer risk: Clinicians' current practice and futures needs. *Breast, 23*(5), 644–650. doi.org/10.1016/j.breast.2014.06.014

Colorado Department of Public Health and Environment. (2016). *Breast cancer.* Retrieved from https://www.colorado.gov/pacific/sites/default/files/CHED_ Cancer_table_Mortality_year_gender_race_0312_0215.pdf

Complete Health Solutions. (2016). *Health care connected*. Retrieved from http://completehealthcaresolutions.com/

Constantino, J. P., Gail, M. H., Pee, D., Anderson, S., Redmond, C. K., Benichou, J., …Weiand, J. S. (1999). Validation studies for models projecting the risk of invasive and total breast cancer incidence. *Journal National Cancer Institute, 91*(18), 1541-1548. doi:10.1093/jnci/91.18.1541

CRA Health. (2016). *Cancer risk assessment*. Retrieved from http://www.crahealth.com/ product-suite-comparison

Cuzick, J., Powles, T., Veronesi, U., Forbes, J., Edwards, R., Ashley, S., & Boyle, P. (2003). Overview of the main outcomes in breast-cancer prevention trials. *Lancet, 361,* 9354, 296-300. doi.org/10.1016/S0140-6736(03)12342-2

Cuzick, J., Sestak, I., Bonanni, B., Costantino, J. P., Cummings. S., DeCensi, A., … Wickerham, D. L. (2013). Selective oestrogen receptor modulators in prevention of breast cancer: An updated meta-analysis of individual participant data. *Lancet, 381*,1827–1834. doi:10.1016/S0140-6736(13)

Cuzick, J., Sestak, I., Forbes, J. F., Dowsett, M., Knox J., Cawthorn S., … Howell, A. (2014). IBIS-II investigators: Anastrozole for prevention of breast cancer in high-risk post-menopausal women (IBIS-II)--An international, double-blind, randomized placebo-controlled trial. *Lancet, 383*,1041–1048. doi:10.1016/S0140-6736(13)62292-8

Day, R., Ganz, P. A., Costantino, J. P., Cronin, W. M. Wickerham, D. L., & Fisher, B. (1999). Health-related quality of life and tamoxifen in breast cancer prevention: A report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of Clinical Oncology,17*, 2659–2669.

DeSantis, C. E., Fedewa, S. A., Goding Sauer, A., Kramer, J. L., Smith, R. A., & Jemal, A. (2015). Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. *CA: A Cancer Journal for Clinicians*, *66*(1), 31-42. doi:10.3322/caac.21320

Doherty, T. M. (2016, March 15). *The future of health is here. An innovative way to engage patients at the point of care.* Retrieved from http://centerfortotalhealth. org/tag/indigo/

Domchek, S. M., & Antoniou, A. (2007). Cancer risk models: Translating family history into clinical management. *Annals of Internal Medicine, 147*(7), 515–517. doi:10.7326/0003-4819-147-7-200710020-00009

Emory University. (2012). *B-RST™ Genetics Referral Screening Tool*. Retrieved from https://www.breastcancergenescreen.org/providers.aspx

Evans, D. G. R., Warwick, J., Astley, S. M., Stavrinos, P., Sahin, S., Ingham, S., ...Beetles, U. (2012). Assessing individual breast cancer risk within the UK National Health Service Breast Screening Program: A new paradigm for cancer prevention. *Cancer Prevention Research, 5*(7), 943-951. doi 10.1158/1940-6207.CAPR-11-0458

Evans, D. G., & Howell, A. (2015). Can the breast screening appointment be used to provide risk assessment and prevention advice? *Breast Cancer Research : BCR, 17*(1), 84. doi.org/10.1186/s13058-015-0595-y

Fine, R. E., Gittleman, M. A., & Kobbermann, A. (2015). *2015 Webinar: ICD 10 implementation* [PowerPoint slides]. Retrieved from https://www.breastsurgeons.org/docs2015/2015_Webinar_ICD_Implementation.pdf

Fisher, B., Costantino, J. P., Wickerham, L., Redmond, C., Kavanah, M., Cronin, W. M., …Wolmark, N. (1998). Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the National Cancer Institute, 90*(18), 1371-1388. doi:10.1093/jnci/90.18.1371

Fisher, B., Costantino, J. P., Wickerham, D. L., Cecchini, R. S., Cronin, W. M., Robidoux, A., …Wolmark, N. (2005). Tamoxifen for the prevention of breast cancer: Current status of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the National Cancer Institute, 97*(22), 1652-1662. doi:10.1093/jnci/dji372

Forrow, L., Taylor, W. C., & Arnold, R. M. (1992). Absolutely relative: How research results are summarized can affect treatment decisions. *American Journal of Medicine, 92*(2), 121–124. doi:10.1016/0002-9343(92)90100-P

Freedman, A. N., Graubard, B. I., Rao, S. R., McCaskill-Stevens, W., Ballard-Barbash, R., & Gail, M. (2003). Estimates of the number of U.S. women who could benefit from tamoxifen for breast cancer chemoprevention. *Journal of the National Cancer Institute, 95,* 526-532. doi:10.1093/jnci/95.7.526

Freedman, A. N., Yu, B., Gail, M. H., Costantino, J. P., Graubard, B. I., Vogel, V. G., …McCaskill-Stevens, W. (2011). Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *Journal of Clinical Oncology, 29,* 2327–2333. doi:10.1200/JCO.2010.33.0258

Gail, M. H., Costantino, J. P., Bryant, J., Croyle, R., Freedman, L., Helzlsouer, K., & Vogel, V. (1999). Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *Journal of the National Cancer Institute, 91,* 1829–1846. doi:10.1093/jnci/91.21.1829

Genetic Home Reference. (2016, September 8). *Health conditions, Breast cancer: Inheritance pattern*. Retrieved from https://ghr.nlm.nih.gov/condition/breast-cancer#statistics

Goetz, M., Kamal, A., & Ames, M. (2008). Tamoxifen pharmacogenomics: The role of CYP2D6 as a predictor of drug response. *Clinical Pharmacology and Therapeutics, 83*(1), 160–166. doi.org/10.1038/sj.clpt.6100367

Goss, P. E., Ingle, J. N., Ales-Martinez, J. E., Cheung, A. M., Chlebowski, R. T., Wactawski-Wende, J, …Richardson, H. (2011). Exemestane for breast-cancer prevention in post-menopausal women. *New England Journal of Medicine, 64*, 2381–2391. doi:10.1056/NEJMoa1103507.

Hasson, F., Keeney, S., & McKenna, H. (2000). Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing, 32*(4), 1008-1015. doi.org.unco.idm.oclc.org/j.1365-2648.2000.t01-1-01567.x10.1046/j.1365-2648.2000.01567.x

Health and Human Services. (2015, December, 18). *Talk with a doctor if breast or ovarian cancer runs in your family*. Retrieved from https://healthfinder.gov/ Health Topics/Category/health-conditions-and-diseases/cancer/talk-with-a-doctor-if-breast-or-ovarian-cancer-runs-in-your-family

Heisey, R., Pimlott, N., Clemons, M., Cummings, S., & Drummond, N. (2006). Women's views on chemoprevention of breast cancer: A qualitative study. *Canadian Family Physician, 52*, 624–625. Retrieved from http://www.ncbi.nlm.nih.gov/ pmc/articles/PMC1531726/

Holmberg, C., Waters, E. A., Whitehouse, K., Daly, M., & McCaskill-Stevens, W. (2015). My lived experiences are more important than your probabilities: The role of individualized risk estimates for decision making about participation in the study of tamoxifen and raloxifene (STAR). *Medical Decision Making, 35*, 1010-1022. doi:10.1177/0272989X15594382

Howell, A., Anderson, A. S., Clarke, R. B., Duffy, S. W., Evans, D. G., Garcia-Closas, M., …Harvie, M. N. (2014). Risk determination and prevention of breast cancer. *Breast Cancer Research. 16*(5), 446. doi:10.1186/s13058-014-0446-2

ICD10Data.com. (2016). *Genetic susceptibility to malignant neoplasm of breast.* Retrieved from http://www.icd10data.com/ICD10CM/Codes/Z00-Z99/Z14-Z15/Z15-/Z15.01

Kaiser Permanente. (2016). *Share our views, news and moves: About Kaiser Permanente*. Retrieved from https://share.kaiserpermanente.org/about-kaiser-permanente/

Kaiser Permanente Healthwise. (2015, November 20). *Breast cancer: What should I do if I'm at high risk? Decision point*. Retrieved from https://healthy.kaiser permanente.org/health/care/consumer/health-wellness/conditions-diseases

Katapodi, M., Dodd, M., Lee, K., & Facione, N. (2009). Underestimation of breast cancer risk: Influence on screening behavior. *Oncology Nursing Forum, 36*(3), 306-314. doi:10.1188/09.ONF.306-314

Keeney, S., Hasson, F., & McKenna, H. (2006). Consulting the oracle: Ten lessons from using the Delphi technique in nursing research. *Journal of Advanced Nursing, 53*(2), 205-212. doi:10.1111/j.1365-2648.2006.03716.x

King, M., Wieland, S., Hale, K., Lee, M., Walsh, T., Owens, K., ….Fisher, B. (2001). Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA, 286*(18), 2251-2256. doi:10.1001/jama.286.18.2251

Kushi, L. H., Doyle, C., McCullough, M., Rock, C. L., Demark-Wahnefried, W., Bandera, E.V., …Gansler, T. (2012). Guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA: A Cancer Journal for Clinicians, 62*(1), 30–67. doi:10.3322/caac.20140

LaCroix, A. Z., Powles, T., Osborne, C. K., Wolter, K., Thompson, J. R., Thompson, D.D., …Vukicevic, S. (2010). Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *Journal of the National Cancer Institute,102*, 1706–1715. doi:10.1093/jnci/djq415

Mahoney, M. C., Bevers, T., Linos, E., & Willett, W. C. (2008). Opportunities and strategies for breast cancer prevention through risk reduction.*CA: A Cancer Journal for Clinicians, 58*(6), 347-371. doi:10.3322/CA.2008.0016

Malenka, D. J., Baron, J. A., Johansen, S., Wahrenberger, J. W., & Ross, J. M. (1993). The framing effect of relative and absolute risk. *Journal of General Internal Medicine, 8*(10), 543–548. doi:10.1007/BF02599636

Melnyk, M., & Fineout-Overholt, E. (Eds.). (2015). *Evidence-based practice in nursing and healthcare: A guide to best practice* (3rd ed.). Philadelphia, PA: Wolters Kluwer.

Mocellin, S. (2016). Risk-reducing medication for primary breast cancer: A network meta-analysis. *Cochrane Database of Systematic Reviews*, 5. doi:10.1002/14651858.CD012191

Moyer, V. A. (2014). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Annals Internal Medicine, 160*(4), 271-281. doi:10.7326/M13-2747

Murff, H. J., Spigel, D. R., & Syngal, S. (2004). Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *Journal of the American Medical Association, 292*(12), 1480-1489. doi:10.1001/jama.292.12.1480

National Cancer Institute. (1999). *Breast cancer risk assessment tool (BCRAT)*. Retrieved from http://www.cancer.gov/bcrisktool/

National Comprehensive Cancer Network. (2016, January). *NCCN guidelines*: *Breast cancer risk reduction NCCN evidence blocks.* Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast_risk_blocks.pdf

National Institute for Healthcare Excellence. (2015). *Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer--Screening for high risk for breast cancer*. Retrieved from http://www.guideline. gov/content.aspx?f=rss&id=46932#Section420

Nelson, H., Fu, R., Griffin, J., Nygren, P., Smith, M., & Humphrey, L. (2009). Systematic review: Comparative effectiveness of medications to reduce risk for primary breast cancer. *Annals of Internal Medicine, 151*(10), 703-226. doi:10.1059/0003-4819-151-10-200911170-00147

Nelson, H. D., Pappas, M., Zakher, B., Mitchell, J. P., Okinaka-Hu, L., & Fu, R. (2014). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: A systematic review to update the U.S. Preventive Services Task Force recommendation. *Annals of Internal Medicine; 160*(4), 255-266. doi:10.7326/M13-1684

Nelson, H. D., Smith, B., Griffin, J. C., & Fu, R. (2013). Use of medications to reduce risk for primary breast cancer: A systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 158*(8), 604-614. doi:10.7326/0003-4819-158-8-201304160-00005

Nelson, H. D., Zacher, B., Cantor, A., Fu, R., Griffin, J., O'Meara, E. S., …Miglioretti, D. L. (2012). Risk factors for breast cancer for women aged 40 to 49 years. *Annals of Internal Medicine*, *156*(9), 635-W-224. doi:10.7326/0003-4819-156-9-201205010-00006

Owens, W. L., Gallagher, T. J., Kincheloe, M. J., & Ruetten, V. L. (2011). Implementation in a large health system of a program to identify women at high risk for breast cancer, *Journal of Oncology Practice, 7*, 285-288. doi:10.1200/JOP.2010.000107

Ozanne, E. M., Drohan, B., Bosinoff, P., Senine, A., Jellinek, M., Cronin, C., …Hughes, K. S (2013). Which risk model to use? Clinical implications of ACS MRI screening guidelines. *Cancer Epidemiology Biomarkers and Prevention. 22*(1), 146-149. doi: 10.1158/1055-9965.EPI-12-0570

Phillips, K., Steel, E. J., Collins, I., Emery, J., Pirotta, M., Mann, G. B., ...Keogh, L. (2016). Transitioning to routine breast cancer risk assessment and management in primary care: What can we learn from cardiovascular disease? *Australian Journal of Primary Health*, *22*(3), 255-261. doi:10.1071/PY14156

Prasad, V., & Diener-West, M. (2015). Primary chemoprevention of breast cancer: Are the adverse effects too burdensome? *Canadian Medical Association Journal, 187*(9), E276-278. doi:10.1503/cmaj.141627

Rondanina, G., Puntoni, M., Severi, G., Varricchio, C., Zunino, A., Feroce, I., ...Decensi, A. (2008). Psychological and clinical factors implicated in decision making about a trial of low-dose tamoxifen in hormone replacement therapy users. *Journal of Clinical Oncology*, *26*(9), 1537-1543. doi: 10.1200/JCO.2007.13.6739

Ropka, M. E., Keim, J., & Philbrick, J. T. (2010). Patient decisions about breast cancer chemoprevention: A systematic review and meta-analysis. *Journal of Clinical Oncology, 28*, 3090–3095. doi:10.1200/JCO.2009.27.8077

Sabatino, S. A., White, M. C. Thompson, T. D., & Klabunde, C. N. (2015, May 8). Cancer screening test use- United States, 2013. *Morbidity and Mortality Weekly Report, MMWR, 64*(17), 464-468. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6417a4.htm#Tab1

Sebelius, K., & Wasserman Schultz, D. (2014, January 10). *More than 2.8 million reasons for hope*. Retrieved from http://www.womenshealth.gov/blog/reasons-for-hope.html

Seidman, A. (2012, March 7). *Exemestane reduces breast cancer risk in high–risk postmenopausal women*. Retrieved from http://www.cancer.gov/types/breast/research/exemestane-reduces-risk

Sestak, I., & Cuzick, J. (2015). Update on breast cancer risk prediction and prevention. *Current Opinion in Obstetrics & Gynecology*, *27*(1), 92-97. doi:10.1097/GCO.0000000000000153

Shah, C., Berry, S., Dekhne, N., Lanni, T., Lowry, H., & Vicini, F. (2012). Implementation and outcomes of a multidisciplinary high-risk breast cancer program: The William Beaumont Hospital experience. *Clinical Breast Cancer, 12*(3), 215-218. doi:10.1016/j.clbc.2012.03.002

Smith, R. A., Manassaram-Baptiste, D., Brooks, D., Doroshenk, M., Fedewa, S., Saslow, D., ...Wender, R. (2015). Cancer screening in the United States, 2015: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA: A Cancer Journal for Clinicians, 65,* 30–54. doi:10.3322/caac.21261

Smith, S. G., Sestak, I., Forster, A., Partridge, A., Side, L., Wolf, M.S., …Cuzick, J. (2016). Factors affecting uptake and adherence to breast cancer chemoprevention: A systematic review and meta-analysis. *Annals of Oncology,27*(4), 575-590. doi:10.1093/annonc/mdv590

Sporn, M. B., Dunlop, N. M., Newton, D. L., & Smith, J. M. (1976, May). Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Federation Proceedings, 35*(6),1332-1338.

Stetler, C. B. (2001). Updating the Stetler model of research utilization to facilitate evidence-based practice. *Nursing Outlook, 49,* 272-279. doi:10.1067/mno.2001.120517

Stuckey, A. R., & Onstad, M. A. (2015). Hereditary breast cancer: An update on risk assessment and genetic testing in 2015. *American Journal of Obstetrics and Gynecology, 213*(2), 161-165. doi.org/10.1016/j.ajog.2015.03.003

Taylor, F., Huffman, M. D., Macedo, A. F., Moore, T. H., Burke, M., Davey Smith, G., ...Ebrahim, S. (2013). *Statins for the primary prevention of cardiovascular disease*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23440795

Tice, J. A., Cummings, S. R., Smith-Bindman, R., Ichikawa, L., Barlow, W. E., & Kerlikowske, K. (2008). Using clinical factors and mammographic breast density to estimate breast cancer risk: Development and validation of a new predictive model. *Annals of Internal Medicine, 148*(5), 337-347. doi:10.7326/0003-4819-148-5-200803040-00004

Traxler, L. B., Martin, M. I., Kerber, A. S., Bellcross, C. A., Crane, B. E., Green, V., … Graham, S. G. A. (2014). Implementing a screening tool for identifying patients at risk for hereditary breast and ovarian cancer: A statewide initiative. *Annals of Surgical Oncology, 21*(10), 3342-3347. doi 10.1245/s10434-014-3921-1

Tyrer, J., Duffy, S. W., & Cuzick, J. (2004). A breast cancer prediction model incorporating familial and personal risk factors. *Statistics in Medicine, 23*(7), 1111-1130. Retrieved from http://www.ems-trials.org/(p 3)

U.S. Preventive Services Task Force. (2013, September). *Breast cancer medications for risk reduction: Recommendation summary*. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-medications-for-risk-reduction?ds=1&s=breast%20cancer

Visvanathan, K., Hurley, P., Bantug, E., Brown, P., Col, N. F., Cuzick, J., …Lippman, S. M. (2013). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 31*, 2942–2962. doi:10.1200/JCO.2013.49.3122.

Vogel, V. G. (2010). Tipping the balance for the primary prevention of breast cancer. *Journal of the National Cancer Institute, 102*, 1–3. doi: 10.1093/jnci/djq435

Vogel, V. G. (2015). Ongoing data from the breast cancer prevention trials: Opportunity for breast cancer risk reduction. *BMC Medicine, 13*(1), 63. doi:10.1186/s12916-015-0300-0

Vogel, V. G., Costantino, J. P., Wickerham, D. L., Cronin, W. M., Cecchini, R. S., Atkins, J. N., …Wolmark, N. (2010). Update of the National Surgical Adjuvant Breast and Bowel Project study of tamoxifen and raloxifene (STAR) P-2 trial: Preventing breast cancer. *Cancer Prevention Research, 3*(6), 696–706. http://doi.org/10.1158/1940-6207.CAPR-10-0076

Waldrop, J., Caruso, D., Fuchs, M. A., & Hypes, K. (2014). EC as PIE: Five criteria for executing a successful DNP final project. *Journal of Professional Nursing, 30*(4), 300-306. doi:org/10.1016/j.projnurs.2014.01.003

Waters, E. A., Cronin, K. A., Graubard, B. I., Han, P. K., & Freedman, A. N. (2010). Prevalence of tamoxifen use for breast cancer chemoprevention among U.S. women. *American Society of Preventive Oncology, 19*, 443–446. doi:10.1158/1055-9965.EPI-09-0930

Williams, S. (2013, February). *Clinical practice guideline: Breast cancer risk*. Retrieved from http://www.providers.kaiserpermanente.org/html/cpp_mas/ clinical library.html?.

APPENDIX A

HEALTHCARE ORGANIZATION INSTITUTIONAL REVIEW BOARD DESIGNATION

KAISER PERMANENTE®

August 15, 2016

Linda M Kottmann, MSN, WHNP-BC
Ob/Gyn Department
Lone Tree Medical Specialty Office
Kaiser Permanente Colorado

RE: Chemoprevention of Primary Breast Cancer for Women at High Risk: Implementing an Evidence Based Recommendation

Dear Ms. Kottmann:

On August 15, 2016, a designated member of the Kaiser Permanente of Colorado (KPCO) Institutional Review Board (IRB) reviewed the documents submitted for the above referenced project. The project does not meet the regulatory definition of research involving human subjects as noted here:

◉ Not Research

The activity does not meet the regulatory definition of research at 45 CFR 46.102(d).

○ Not Human Subject

The activity does not meet the regulatory definition of a human subjects at 45 CFR 46.102(f).

Therefore, the project is not required to be reviewed by a KP Institutional Review Board (IRB). This determination is based on the information provided. If the scope or nature of the project changes in a manner that could impact this review, please resubmit for a new determination. Also, you are responsible for keeping a copy of this determination letter in your project files as it may be necessary to demonstrate that your project was properly reviewed.

This notification is only informing you about the outcome of the Human Subjects Research determination form. There may be other institutional approvals required before this project may move forward (e.g. KP-IT, Operations, Compliance).

Please feel free to call me at (303)614-1342 if you have any questions regarding this notification.

Thank you,

Melissa Goff
Compliance Senior Manager, IRB

45CFR46.102(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
45CFR46.102(f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains(1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

Statement of Mutual Agreement

University of Northern Colorado

Doctorate of Nursing Practice Capstone Project

Linda M Kottmann

December 2, 2015

The purpose of the "Statement of Mutual Agreement" is to describe the shared view between Kaiser Permanente Health Plan of Colorado and Linda M. Kottmann, DNP Candidate from University of Northern Colorado, concerning his/her proposed capstone project.

Proposed Project Title: Closing Gaps in Care: Quality Improvement for Optimal Breast Cancer Screening In a Managed Care Organization

Brief Description of Proposed Project:

The capstone project involves an evaluation of problem areas in screening for breast cancer, and development and implementation of solutions to gaps in care as determined by the interdisciplinary Women's Quality Council Breast Screening Work Group. Anticipated outcomes are improved communication of member's risk status, identification of women at high risk for breast cancer, interdisciplinary coordination of screening, development of an approach to tracking women at high risk, and a revised clinical practice guideline for breast cancer screening.

Goal of Capstone Project: To improve population screening for breast cancer and enhance systems to identify, personalize care for, and track high risk women.

Proposed On-site Activities: Quality improvement measures, committee work, revision of guidelines, update to mammography intake form, adoption of evidenced – based breast cancer screening tool for our organization, use of informatics to facilitate patient centered care.

Confidentiality of Patient Records: Member data will only be used in the aggregate, for example, an evaluation of numbers of women screened who are high risk.

The designated Capstone Community/Agency member, Kimberly Campbell, MD, will agree to participate in the review and approval of the proposal and presentation of the final version of the project. She will attend (on campus or remotely) the meetings for both.

The DNP Capstone project will include a final report, an abstract, potential publication or oral presentation of the report. No personal identifiers will be included and all data will be reported in aggregate form. The author welcomes any comments or suggestions from the Agency, but

reserves the right to publish findings and analysis according to professional standards and principles of academic freedom. For any work of a scholarly nature, the Author agrees to follow the Agency preferences in how it is to be named (or not) in the work.

1/24/16

Signature of Linda M Kottmann, DNP Student Date

1/25/16

Signature of Agency Member, Antigone Parrish, MD, Regional Department Value Advisor, Women's Health, Kaiser Permanente Colorado
Date

1/29/16

Signature of DNP Capstone Chair, Kathleen N Dunemn, PhD Date

APPENDIX B

UNIVERSITY OF NORTHERN COLORADO
INSTITUTIONAL REVIEW BOARD
APPROVAL

UNIVERSITY OF
NORTHERN COLORADO

Institutional Review Board

DATE:	September 12, 2016
TO:	Linda Kottmann, DNP
FROM:	University of Northern Colorado (UNCO) IRB
PROJECT TITLE:	[860381-1] Chemoprevention of Primary Breast Cancer for Women at High Risk: Implementing an Evidence Based Recommendation
SUBMISSION TYPE:	New Project
ACTION:	APPROVAL/VERIFICATION OF EXEMPT STATUS
DECISION DATE:	September 12, 2016
EXPIRATION DATE:	September 12, 2020

Thank you for your submission of New Project materials for this project. The University of Northern Colorado (UNCO) IRB approves this project and verifies its status as EXEMPT according to federal IRB regulations.

Linda -

Thank you for patience with the UNC IRB process. Your application is verified/approved exempt with no requests for amendments or additional materials.

Best wishes with your study.

Sincerely,

Dr. Megan Stellino, UNC IRB Co-Chair

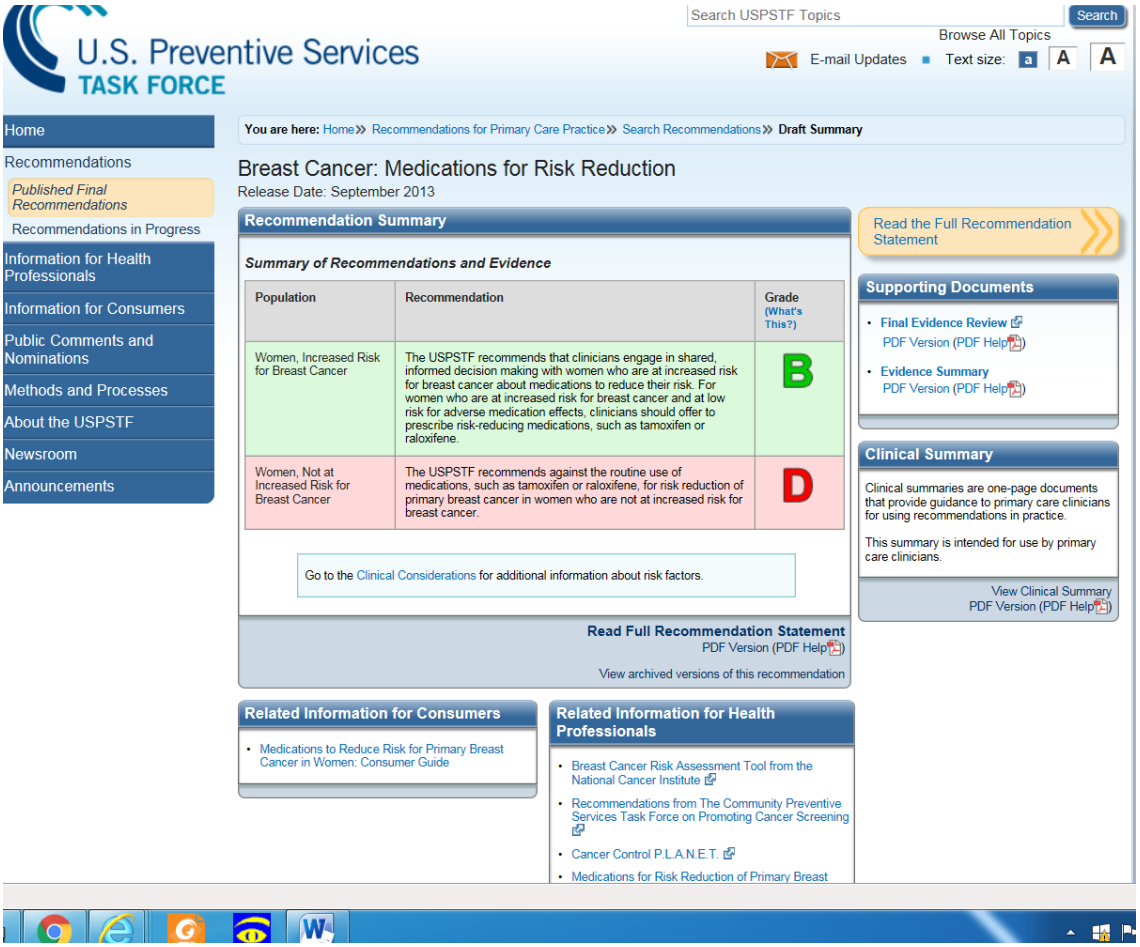
We will retain a copy of this correspondence within our records for a duration of 4 years.

If you have any questions, please contact Sherry May at 970-351-1910 or Sherry.May@unco.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Northern Colorado (UNCO) IRB's records.

APPENDIX C

U.S. PREVENTIVE SERVICES TASK FORCE GRADE B RECOMMENDATION BREAST CANCER: MEDICATIONS FOR RISK REDUCTION



Agency for Healthcare Research and Quality, 2013

Nelson et al. (2014).

Definitions:

What the U.S. Preventive Services Task Force (USPSTF) Grades Mean and Suggestions for Practice

Grade	Grade Definitions	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be measured.	Read "Clinical Considerations" section of USPSTF Recommendation Statement (see the "Major Recommendations" field). If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Agency for Healthcare Research and Quality, 2013.

APPENDIX D

CONSENT FORM FOR HUMAN PARTICIPATION IN RESEARCH

Informed Consent - No signature document (Kaiser Permanente Colorado/ University of Northern Colorado)

CONSENT FORM FOR HUMAN PARTICIPATION IN RESEARCH

UNIVERSITY OF NORTHERN COLORADO

Project title: Chemoprevention of Primary Breast Cancer for Women at High Risk: Implementing an Evidence Based Recommendation

Student: Linda M. Kottmann, MSN, APRN (DNP student)
Academic Advisor Kathleen N. Dunemn, PhD, CNM, University of Northern Colorado School of Nursing Phone number: (970) 351-3081/ (803) 409-8391
e-mail: kathleen.Dunemn@unco.edu
Project advisor: Kimberley Campbell, MD, Colorado Permanente Medical Group

Expert Consensus via a Delphi Study

The purpose of this capstone project is to evaluate the evidence on chemoprevention for primary breast cancer risk reduction; assess the health care organization's current state of use of these medications to prevent breast cancer in women at high risk for the disease; and to evaluate the applicability of the 2013 U.S. Preventive Service Task Force recommendation to offer chemoprevention to women at high risk for primary breast cancer in our clinical environment. Planning how to implement the recommendation as a clinical practice guideline and evaluate outcomes is the final phase of this project.

The Delphi method is a structured communication method that utilizes a questionnaire to survey experts in two or more rounds. Information from the literature review on chemoprevention for primary breast cancer in women at high risk is used to develop the first round of questions regarding the 2013 U.S Preventive Services Task Force recommendation. The response from the first round will be anonymously shared with participants in the second round. Participants will gain additional knowledge through the shared responses of their colleagues. Anonymity reduces the impact of feelings of embarrassment, judgements, fear of repercussions, the bandwagon effect, and influences of personalities dominating the process. The Delphi method has been used in healthcare and other industries and is of value where there is uncertainly or lack of empirical knowledge. It is anticipated that two or three rounds will be necessary but not more than four rounds. All Delphi surveys will be sent and returned electronically within the firewall on the intranet. It is expected that each participant wild spend approximately 15-20 minutes to complete each round of the Delphi process.

The purpose of this e-mail is to invite your participation. Participation is voluntary and all responses will be kept anonymous. The data collected will be kept on a password protected thumb drive that is accessible only by the nurse practitioner (DNP student) and her advisor. There are no foreseeable risks to participants. This is a quality improvement project to evaluate the evidence for breast cancer chemoprevention and applicability of the 2013 U.S Preventive Service Task Force's Breast Cancer: Medications for Risk

Reduction recommendation in the clinical setting. Past and existing patients will not benefit from this project as there is no direct intervention. The potential benefit for future patients is improved knowledge of risk reduction strategies for women at high risk of breast cancer. Future clinicians may benefit from having a clinical recommendation to follow.

Participation is voluntary. If you begin to participate, you may decide to stop or withdraw at any time. Your decision will be respected and will not result in a loss of benefits to which you are otherwise entitled. If you have any questions, please contact one of the undersigned.

Having read the above document and having had an opportunity to ask any questions, please access and complete the attached document, "Phase One: Delphi Study Round One Questions." Please return the completed survey to me, Linda.M.Kottmann@kp.org. Thank you for participating in our survey. Your feedback is important.
For my Doctoral of Nursing Practice capstone project, I am evaluating whether KP Colorado providers discuss and offer medications for primary breast cancer risk reduction for women at high risk of breast cancer. In September 2013 the U.S Preventive Services Task Force published a recommendation summary as Grade B evidence "that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medications effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene." As a subject matter expert I request your opinions to the following questions.
Using a Delphi method I will gather the responses and submit them back to you for a second round to seek consensus on the process of offering risk reduction medication for women at high risk of breast cancer at Kaiser Permanente Colorado.

Link to the recommendation:
www.uspreventiveservicestaskforce.org/BrowseRec/Search?s=breast (copy and paste in your browser)

P**lease respond by September 15, 2016**

APPENDIX E

ROUND ONE DELPHI SURVEY QUESTIONS

Kottmann DNP capstone

Chemoprevention for Primary Breast Cancer Risk Reduction for Women at High Risk: Evidence Based Rec

1. What is your career title/role?

- [ ] MD/DO
- [ ] APN
- [ ] PA
- [ ] PharmD
- [ ] RN
- [ ] Administrator

Other (please specify)

2. In which discipline do you primarily work?

- ( ) Family Medicine
- ( ) Internal Medicine
- ( ) Nursing
- ( ) OB/Gyn
- ( ) Oncology
- ( ) Pharmacology
- ( ) Radiology/Medical Imaging
- ( ) Surgery
- ( ) Administration

3. At which Denver-Boulder location do you primarily work?

- ( ) North
- ( ) Central
- ( ) South

4. In your opinion are we reaching women at high risk for breast cancer with information to help reduce their risk for incident breast cancer?

- ◯ No
- ◯ Yes

please explain your answer

5. Are medications for primary breast cancer risk reduction being offered/provided at Kaiser Permanente Colorado?

- ◯ No
- ◯ Yes
- ◯ I don't know

6. What is your understanding of current use of selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) for primary breast cancer risk reduction at Kaiser Permanente Colorado?

- ◯ Should not be recommended
- ◯ Rarely offered
- ◯ Should be recommended more frequently than is currently
- ◯ Offered by providers in my discipline
- ◯ Offered by providers in another discipline

7. If risk reducing medications are currently discussed and prescribed which discipline is doing this? (can choose more than 1 answer)

- ☐ Family Medicine
- ☐ Internal Medicine
- ☐ OB/Gyn
- ☐ Oncology
- ☐ Pharmacy
- ☐ Radiology/Medical Imaging
- ☐ Surgery

8. How well is the existing process working?

- I don't know
- Poorly
- Adequately
- Well

9. Do you feel comfortable educating women at high risk of breast cancer to consider chemoprevention?

- Yes
- No

10. Do you feel comfortable prescribing SERMs or AIs to reduce the risk of primary breast cancer in high risk women?

- No
- Yes

comments

11. If the 2013 U.S. Preventive Services Task Force recommendation (Grade B evidence) that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medication to reduce their risk were undertaken in KPCO, how do you envision the process?
Who provides this care?
What barriers would need to be addressed?
What have you seen done that could be applied with our members?

12. Are there any other comments about the USPSTF recommendation Breast Cancer: Medications for Risk Reduction that would like to make?

APPENDIX F

ROUND TWO DELPHI SURVEY QUESTIONS

Chemo-prophylaxis for primary breast cancer for women at high risk round 2

Introduction to 2nd round

Thank you for participating. If you did not answer the first survey your opinion as a subject matter expert in women's health is still valued for this round of the Delphi process. If you get a message that the survey is closed, it means someone else is accessing it at the same time and you are blocked out. If you send me a message at Linda.M.Kottmann@kp.org I can send you an active link.

We had responses from Administration, Family Medicine, Ob/Gyn, Oncology, Radiology, and Surgery. We hope to have participation from Internal Medicine and Pharmacy.

The goal of this round of questions is to build consensus toward the formation of a Clinical Practice Guideline for risk reducing medication for women at high risk for primary breast cancer due to personal history of atypical hyperplasia or LCIS on a breast biopsy, significant family history of breast or ovarian cancer (especially among first-degree relatives and onset before age 50 years), known personal or familial genetic mutations that increase risk, or "those women that have the alternating every 6 months mammogram and breast MRI" as one of my colleagues has said. In general women who have an equal or greater than 20% lifetime risk of breast cancer or a Gail risk of greater than 1.7% risk in the next five years. The 2013 USPSTF Grade B recommendation Breast Cancer; Medications for Risk Reduction:

Recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene.
The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. (Grade B evidence)

This guideline proposed would not delete or interfere with but support the need for referrals to genetic counseling, intensive surveillance, or risk reducing surgery for appropriate women. Risk reducing medications are another option for high risk women.

As a Subject Matter Expert, please respond to the following questions:

1. The majority of respondents felt KPCO is not reaching women at high risk for breast cancer with information to reduce their risk. Would you agree that having a prompt in Health Trac that screens for high risk status is something you would use?

- Yes
- No

Other (please specify)

2. Participants from round 1 felt that KPCO should recommend selective estrogen receptor modulators or aromatase inhibitors for primary breast cancer risk reduction to high risk women at KPCO. Would you agree that the USPSTF recommendation to discuss and offer SERMs and AIs for selected high risk women is a reasonable course of care?

- yes
- no

Other (please specify)

3. Many responded that lack of knowledge about medications for primary breast cancer risk reduction and their benefits & risks were barriers to counseling women about these options. What would be the most effective way to gain this knowledge?

- Departmental in service
- Webinar
- Office champions

Other (please specify)

4. The majority of respondents indicated that oncology is the primary group to discuss and prescribe SERMs and AIs for risk reduction. Would you support that primary care and Ob/Gyn, with appropriate training, can and should initiate these discussions with high risk women?

- Yes
- No

Other (please specify)

5. Many respondents suggested having specific guidelines for discussions with members about SERMs and AIs for risk reduction.
A clinical practice guideline would indicate the mechanism for identifying women at high risk, and when that risk status will be reassessed;
inclusion / exclusion criteria;
the medication appropriate for the woman based on her menopausal and health risk status;
dosage, and risks/benefits, and alternatives to the medication,
length of time of medication use;
and management of side effects.
Do you agree this forms the basis of a guideline?
If no, what needs to be included?

- yes
- no

Other (please specify)

6. For planning purposes if support is needed for these discussions with members, or the woman desires a 2nd opinion, who would we refer to?

- Pharmacy
- Oncology
- Ob/Gyn
- Primary Care physician
- Genetics

Other (please specify)

7. Are there other comments you would like to make about developing a guideline on this topic at KPCO?

- No
- Yes

Other (please specify)

Thank you for your participation in this survey. If you have questions or comments for me that were not addressed please contact me at Linda.m.Kottmann@kp.org, or 303 649 5581 or KP Skype or Sametime.

APPENDIX G

CLINICAL PRACTICE GUIDELINE: KAISER PERMANENTE COLORADO

CLINICAL PRACTICE GUIDELINE KAISER PERMANENTE COLORADO

Risk-Reducing Medications (formerly called chemoprevention) for Women at High Risk of Breast Cancer.

Reviewed	November, 2016
Target Population	Women at high risk of primary breast cancer (no prior personal breast cancer history) aged 30 or older.
Author	Linda Kottmann, WHNP-BC, Breast Cancer Screening Work Group of the Women's Heath Quality Council

Reviewed/Approved by (pending Tig Parrish, MD, RVA, Kim Campbell, MD)

1. Overview:

High risk is defined as a Gail -2 BCRAT (www.cancer.gov/BCRAT) 5 year risk score equal or greater than 1.7% , or a lifetime risk score equal or greater than 20%. (refs).

To use risk reducing medications **the USPSTF (2013) recommends a 5 year risk score of 3%** or greater (*not* 1.7%, Nelson et al, 2013).

Beginning in the winter of 2017 Radiology/Medical Imaging is launching a new software system called MagView that asks for breast cancer risk factors using the BRCAPRO tool. This will calculate risk scores for women obtaining mammograms.

For younger women or those who have not had a mammogram a risk assessment will be done in Health Connect (B-RST or "Gail -2" BCRAT) beginning at age 30 and repeated every 5 years. Women who have had ionizing mantle radiation treatment to their chest at less than age 30 (primarily for Hodgkin's lymphoma) are considered high risk for breast cancer and should be managed according to the Clinical Practice Guideline for high risk women (see Breast Cancer Screening Clinical Practice Guideline February 2013 - KP link, and Inherited Susceptibility to Breast and/or Ovarian Cancer CPG, July, 2013-KP link).

2. **The 2013 U.S. Preventive Services Task Force (USPSTF) Breast Cancer: Medication for Risk Reduction Recommendation:**

Breast Cancer: Medications for Risk Reduction
Release Date: September 2013

Summary of Recommendations and Evidence

Population	Recommendation	Grade B
Women, Increased Risk for Breast Cancer	The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene.	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
Women, Not at Increased Risk for Breast Cancer	The USPSTF recommends against the routine use of medications, such as tamoxifen or raloxifene, for risk reduction of primary breast cancer in women who are not at increased risk for breast cancer.	Grade D The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits

https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-medications-for-risk-reduction

3. A suggested algorithm for medication selection

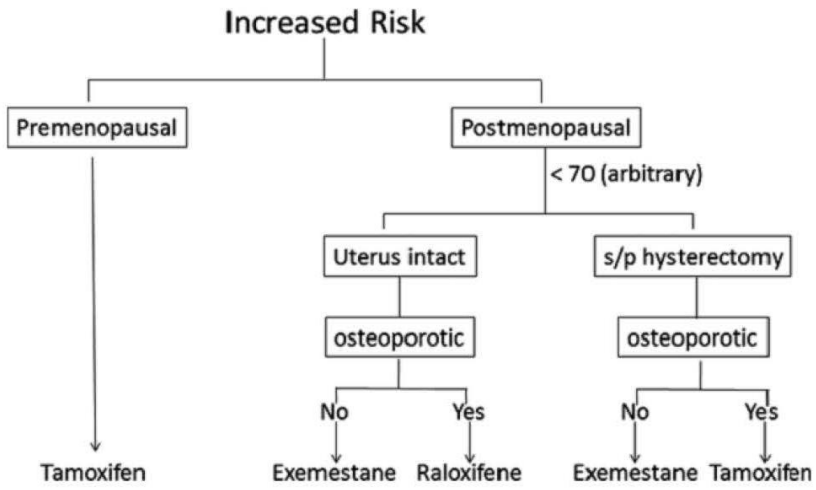


Figure 1. A suggested decision tree for chemoprevention.

Algorithm from Euhus & Diaz, 2014, p. 78.

4. Evidence for the recommendation for medications to reduce breast cancer risk in women determined to be at high risk.

Meta-analysis of randomized studies indicates primary invasive breast cancer and DCIS can be reduced by 38% through the use of selective estrogen receptor modulators, tamoxifen and raloxifene (Cuzick et al, 2013).

Medication & duration	NNT to prevent 1 case of IBC	Data source
Tamoxifen 5 years	47	Fisher et al., 1998, NSABP, BCPT
Raloxifene 4 years	93 -112-125	Cauley et al., 2001, MORE, CORE, RUTH
Exemestane 3 years	94	Goss et al., 2011 MAP.3
Exemestane 5 years	26	Goss et al., 2011
Anastrozole 7 years	36	IBIS-II

These numbers are comparable to the NNT for interventions commonly recommended by primary care physicians, for example, the NNT with statins for the primary prevention of myocardial infarction is 60 (Advani & Morena – Aspitia, 2014).

A *Cochrane Database of Systemic Reviews* analysis indicates that the aromatase inhibitors, exemestane and anastrozole, decrease primary breast cancer in post-menopausal high risk women (Mocellin, 2016). Exemestane decreased primary breast cancer incidence by 65% at 35 months (Goss, et al., 2011) and anastrozole decreased primary breast cancer by 53% (Cuzick et al., 2014).

Despite a reduction in breast cancer incidence with these medications *they have not been proven to decrease breast cancer deaths.*

(1) Selective estrogen receptor modulators (SERMs)

a) **Tamoxifen** – 1st choice for women 35 yo +.

- **Effective for reductions in ER + breast cancer, no effect on ER negative breast cancers.**
- **Contraindications**: history of DVT, PE, stroke, transient ischemic attack, during prolonged immobilization, or in women who are pregnant, may become pregnant, or are breastfeeding, or have undiagnosed uterine/vaginal bleeding.
- May be preferred for women without a uterus due to an increased risk of endometrial cancer. (RR 1.24 STAR data)
- Cannot be taken with OCP or HRT.
- Has no effect on breast cancer risks for *BRCA1 mutation* carriers as breast cancer in these women tends to be estrogen receptor negative cancers. **Women with *BRCA1* and *BRCA2* mutations receive greater risk reduction with oophorectomy or mastectomy; refer to OB/Gyn physicians and/or surgery.**

1. Dosage Tamoxifen 20 mg q d for 5 years

1). Harms

Risk endometrial cancer, DVT, PE, VTE, stroke, cataract.
See table

b) **Raloxifene** – 1st line for post-menopausal women with osteoporosis.

- Not recommended for pre-menopausal women

- Slightly less effective at reducing primary breast cancer but better tolerated for most women.
- Does not prevent noninvasive breast cancers.
- 30% less thromboembolic events compared to tamoxifen (Vogel, Costantino, Wickerham et al, 2006)

1. Raloxifene Dosage 60 mg q d for 5 years.

1) Harms

Risk VTE

Smart RX link to orders in Health Connect

Dropdown Tamoxifen 20 mg po q day, # 60 , prn refills

Raloxifene 60 mg po q day # 60, prn refills

Advice referral Oncology

Referral Oncology

Advice referral Genetics

Referral Genetics

Advice referral surgery

Referral surgery

Advice referral Ob/Gyn

Referral Ob/Gyn

(2) Aromatase Inhibitors (AIs). Only for postmenopausal women, avoid in women with osteoporosis as AIs decrease bone density.

c) **Exemestane (Aromasin)** – The American Society of Clinical Oncology (2013) recommends use for risk reduction through a clinical trial only. Refer to Oncology.

1. Dosage 25 mg q d for 5 years

d) **Anastrozole (Arimidex)** –

1. Dosage 1 mg q d for 5 yrs

(3) Medication cost and coverage. HHS indicates medication are covered for high risk women. Recommend member check her coverage with financial counseling at 303 338 3025.

(4) Women determined to be at high risk for primary breast cancer should be offered genetic counseling as appropriate, see Clinical Practice Guideline Inherited Susceptibility to Breast and/or Ovarian Cancer, July, 2013 (add link).

(5) **Women with known *BRCA1* and *BRCA2* mutations obtain greater risk reduction with prophylactic mastectomy and/ or oophorectomy and should be referred to Surgery and/or Ob/Gyn for consultation**. (stated above)

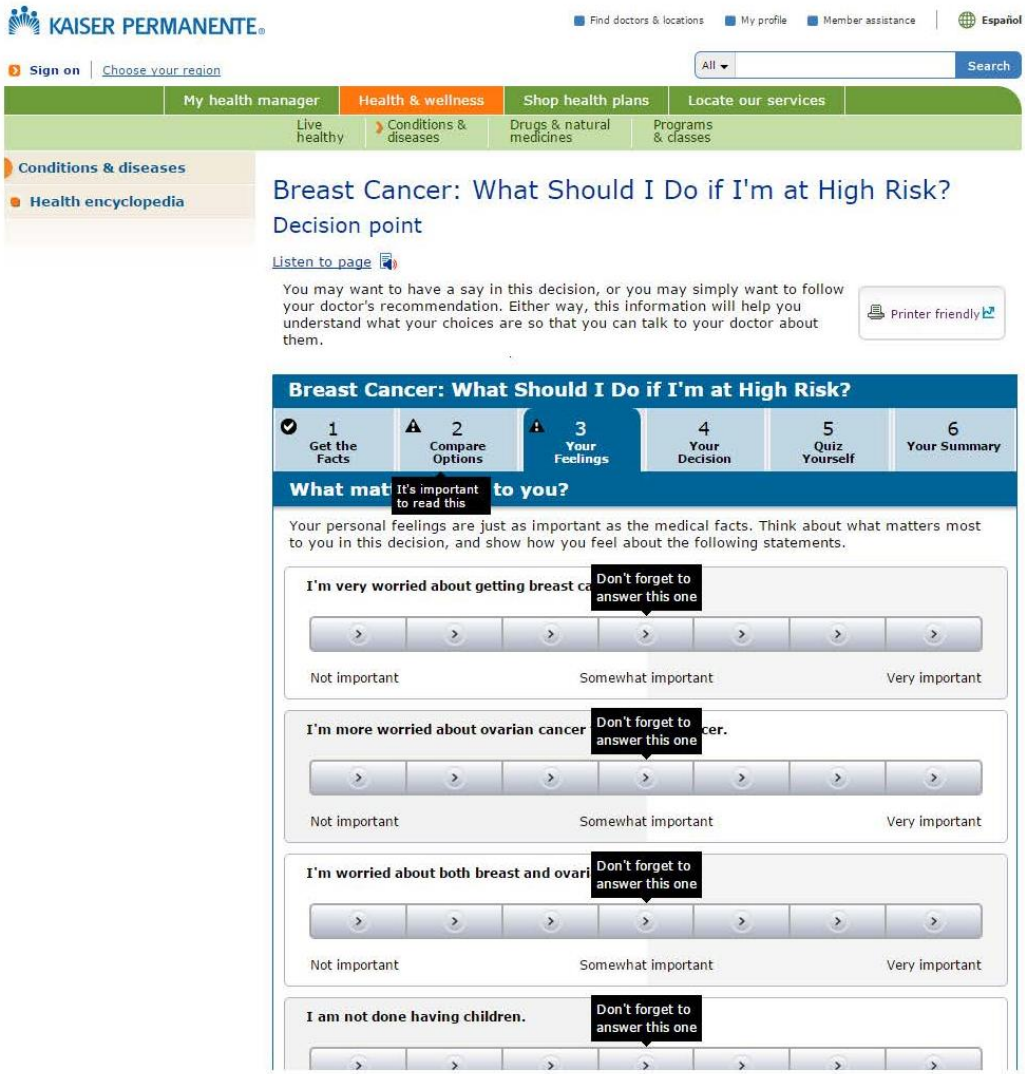
(6) Translating risk terms into meaningful information for members:

* Use "risk –reducing" terminology instead of "chemo-prevention". In studies women have equated chemoprevention or chemoprophylaxis to cancer treatment (Holmberg et al., 2015).

* Use absolute risk where possible, "4 to 5 out of 1000 women will develop uterine cancer with tamoxifen use," instead of tamoxifen doubles uterine cancer risk (Butow & Philips, 2016)

* Refer members to KP.org website for information: **Breast Cancer: What should I do if I'm at High Risk? For a decision making guide**

https://healthy.kaiserpermanente.org/health/care/consumer/health-wellness/conditions-diseases



(7) Management of side effects

Postmenopausal women on tamoxifen must be advised to seek gynecology evaluation if any vaginal bleeding occurs. Premenopausal women treated with tamoxifen have no higher risk of endometrial cancer than women on placebo (ACOG Committee, 2014).

Although many women and clinicians fear endometrial cancer as a side effect of

tamoxifen the majority of endometrial cancers are curable (stage 1/ grade 1)and manifest with uterine bleeding that prompts an evaluation; whereas death is more likely from recurrent breast cancer.

(8) High risk women (lifetime risk > 20%) need ongoing intensive screening: alternating mammogram and breast MRI every 6 months.

(9) Documentation ICD- 10 codes, high risk for breast cancer

Family history of malignant neoplasm of breast	*Z80.3*
Genetic susceptibility to malignant neoplasm of breast	*Z15.01*
Family history of carrier of genetic disease	*Z84.81*
Lobular carcinoma of breast in situ of unspecified breast	*D05.00*
Lobular carcinoma in situ of right breast	*D05.01*
Lobular carcinoma in situ of left breast	*D05.02*
Atypical ductal hyperplasia (ADH)	*610.8x Atypical ductal hyperplasia unspecified (right 1x, left 2x)*
Atypical ductal hyperplasia, right breast	*610.1x*

- Breast Cancer Risk assessment
- Add to Problem list

Additional evidence for risk-reducing medication. American Society of Clinical Oncology Clinical Practice Guideline (*Journal of Clinical Oncology,* August 10, 2013, http://jco.ascopubs.org/content/31/23/2942/T1.expansion.html)

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline

Summary of Clinical Practice Guidelines

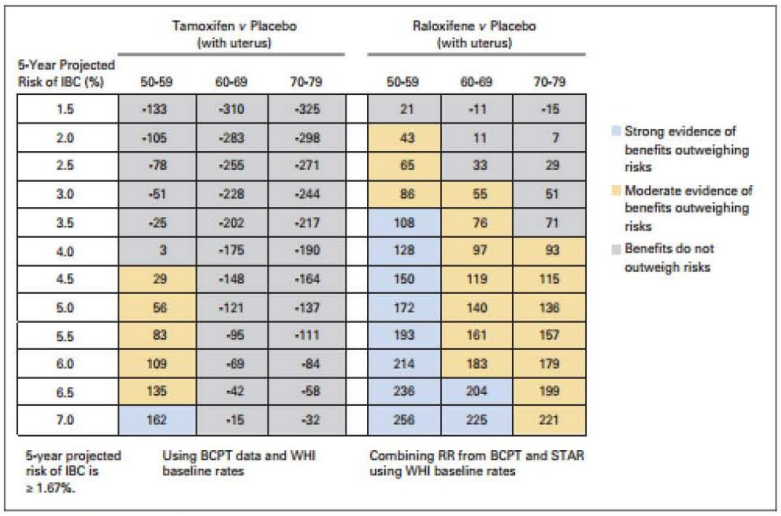
Agent	Old Recommendations (2009)	New Recommendations	Strength of Recommendation and Strength of Evidence
Tamoxifen	May be offered to reduce the risk of ER-positive invasive BC for premenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in premenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66%[e] or with LCIS. Risk reduction benefit continues for at least 10 years.	Strong, evidence-based recommendation.
	May be offered to reduce the risk of ER-positive invasive BC for postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66% or with LCIS. Risk reduction benefit continues for at least 10 years.	Strength of evidence: Strong evidence, based on five RCTs with low risk of bias.
	Is not recommended for women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.	
	Combined use of tamoxifen for BC prevention and hormone therapy is currently not recommended. **Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter,** with a timely workup of abnormal vaginal bleeding.	Is not recommended in combination with hormone therapy. *Is not recommended for women who are pregnant, women who may become pregnant, or nursing mothers.* Follow-up should include a timely workup of abnormal vaginal bleeding.	
	Risks and benefits should be given careful consideration during the decision-making process.	Discussions with patients and health care providers should include both the risks and benefits of tamoxifen in the preventive setting.	

	Dosage: 20 mg per day for 5 years.	Dosage: 20 mg per day orally for 5 years.	
Raloxifene	May be offered to reduce the risk of ER-positive invasive BC in postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Impact on BC mortality is unknown.	*Should be discussed as an option* to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women who are *age ≥ 35 years* with a 5-year projected *absolute* BC risk ≥ 1.66% or with LCIS.	Strong, evidence-based recommendation.
	May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit.	May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit.	
	Should not be used for BC risk reduction in premenopausal women.	Should not be used for BC risk reduction in premenopausal women.	Strength of evidence: Strong evidence, based on four RCTs with low risk of bias.
	Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.	Is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.	
	Risks and benefits should be given careful consideration during the decision-making process.	Discussions with patients and health care providers should include both the risks and benefits of raloxifene in the preventive setting.	
	Dosage: 60 mg per day for 5 years.	Dosage: 60 mg per day orally for 5 years.	
Exemestane	Use [of aromatase inhibitors] **is not recommended outside of the clinical trial setting to lower BC risk.**	*Should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women age ≥ 35 years with a 5-year projected absolute BC risk ≥ 1.66% or with LCIS or atypical hyperplasia.*	Moderate, evidence-based recommendation.
		Should not be used for BC risk reduction in premenopausal women.	
		Discussions with patients and health care providers should include both the risks and benefits of exemestane in the preventive setting.	Strength of evidence: Moderate evidence, based on one RCT with low risk of bias.
		Dosage: 25 mg per day orally for 5 years.	

Abbreviations: ASCO, American Society of Clinical Oncology; BC, breast cancer; ER, estrogen receptor; FDA, US Food and Drug Administration; LCIS, lobular carcinoma in situ; NCI, National Cancer Institute; RCT, randomized controlled trial.

For color coded risk/benefit index for Caucasian, African American and Hispanic women with and without a uterus:

See Freedman A.N., Yu, B., Gail, M.H., Costantino, J.P., Graubard, B.I., Vogel, V.G.,…& McCaskill-Stevens, W. (2011). Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *Journal of Clinical Oncology, 29*, 2327–2333. Doi **10.1200/JCO.2010.33.0258** http://jco.ascopubs.org/content/29/17/2327.full.pdf+html



5-Year Projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50-59	60-69	70-79	Raloxifene *v* Placebo (with uterus) 50-59	60-69	70-79
1.5	-133	-310	-325	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-228	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	138
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

Fig 1. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic with a uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her pr of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights c ife-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and d hrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women m expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening ev example, in this table, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects ife-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > .9$; blue) that the of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events ($P <$ BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

Appendix Table 1. **Results of Primary Prevention Trials**

Outcome	Raloxifene vs. Tamoxifen		Tamoxifen vs. Placebo				Raloxifene vs. Pla		
	RR (95% CI)	Events Reduced or Increased (95% CI), *n**	RR (95% CI)	Trials, *n*†	Placebo Rate (±SE)‡	Events Reduced or Increased (95% CI), *n**	RR (95% CI)	Trials, *n*†	Placebo Rat (±SE)‡
Benefits									
Invasive breast cancer	1.24 (1.05–1.47)§	5 (1–9) fewer with tamoxifen	0.70 (0.59–0.82)	4	4.70 ± 1.02	7 (4–12) fewer with tamoxifen	0.44 (0.27–0.71)	2	3.19 ± 0.5
ER+ breast cancer	0.93 (0.72–1.24)‖	–	0.58 (0.42–0.79)	4	3.67 ± 0.78	8 (3–13) fewer with tamoxifen	0.33 (0.18–0.61)	2	2.45 ± 0.4
ER− breast cancer	1.15 (0.75–1.77)‖	–	1.19 (0.92–1.55)	4	–	–	1.25 (0.67–2.31)	2	–
Noninvasive breast cancer	1.22 (0.95–1.59)§	–	0.85 (0.54–1.35)¶	4	–	–	1.47 (0.75–2.91)	2	–
Breast cancer mortality	0.36 (0.08–1.21)§	–	1.07 (0.66–1.74)	4	–	–	NR**		–
All-cause mortality	0.84 (0.70–1.02)§	–	1.07 (0.90–1.27)	4	–	–	0.84 (0.64–1.10)††	2	–
Vertebral fracture	0.98 (0.65–1.46)‖	–	0.75 (0.48–1.15)‡‡		–	–	0.61 (0.54–0.69)	2	3.45 ± 0.3
Nonvertebral fracture	NR	–	0.66 (0.45–0.98)‡‡		1.55 ± 0.20	3 (0.2–5) fewer with tamoxifen	0.97 (0.87–1.09)	2	–
Harms									
Thromboembolic events‖‖	0.75 (0.60–0.93)§	4 (1–7) more with tamoxifen	1.93 (1.41–2.64)	4	0.91 ± 0.19	4 (2–9) more with tamoxifen	1.60 (1.15–2.23)	2	2.34 ± 0.2
DVT	0.72 (0.54–0.95)§	3 (1–5) more with tamoxifen	1.45 (0.89–2.37)	2	–	–	1.91 (0.87–4.23)	2	–
PE	0.80 (0.57–1.11)§	–	2.69 (1.12–6.47)	2	0.19 ± 0.07	2 (0.1–6) more with tamoxifen	2.19 (0.97–4.97)	2	–
CHD events	1.10 (0.85–1.43)‖	–	1.00 (0.79–1.27)	4	–	–	0.95 (0.84–1.06)	2	–
Stroke	0.96 (0.64–1.43)‖	–	1.36 (0.89–2.08)	4	–	–	0.96 (0.67–1.38)	2	–
Endometrial cancer	0.55 (0.36–0.83)§	5 (2–9) more with tamoxifen	2.13 (1.36–3.32)	3	0.75 ± 0.15	4 (1–10) more with tamoxifen	1.11 (0.65–1.89)††	3	–
Cataracts	0.80 (0.72–0.95)§	15 (8–22) more with tamoxifen	1.25 (0.93–1.67)¶¶	3	–	–	0.93 (0.84–1.04)	2	–

CHD = coronary heart disease; DVT = deep venous thrombosis; ER− = estrogen receptor–negative; ER+ = estrogen receptor–positive; NR = not reported; NSABP = National Surgical Adju
PE = pulmonary embolism; RR = risk ratio; RUTH = Raloxifene Use for the Heart; STAR = Study of Tamoxifen and Raloxifene.
* Numbers of events reduced for benefits or increased for harms compared with placebo or other comparator per 1000 women, assuming 5 y of use.
† If meta-analysis.
‡ Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.
§ Updated results from STAR (22).
‖ Initial results from STAR (48).
¶ Significantly reduced in NSABP P-1 (60 vs. 93 events; RR, 0.63 [CI, 0.45–0.89]) (8).
** 2 breast cancer deaths in 7601 women for raloxifene vs. 0 in 7633 women for placebo (Grady et al, 2010 [50]).
†† Updated meta-analysis.
‡‡ NSABP P-1 (8).
§§ Estimated from the placebo group of the RUTH trial (7).
‖‖ Includes DVT and PE.
¶¶ Significantly increased in NSABP P-1 (574 vs. 507 events; RR, 1.14 [CI, 1.01–1.29]) (11).

References

Advani, P & Moreno-Aspitia, A. (2014). Current strategies for the prevention of breast cancer. *Breast Cancer: Targets and Therapy, 6*, 59 - 71, doi.10.2147/BCTT.S39114

Cuzick J., Sestak I., Bonanni B., Costantino J.P., Cummings S, DeCensi A., … Wickerham, D.L. (2013). Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *Lancet, 381*,1827–1834. Doi: 10.1016/S0140-6736(13)

Cuzick J., Sestak I., Forbes J.F., Dowsett M., Knox J., Cawthorn S., … & Howell A. (2014). IBIS-II investigators: Anastrozole for prevention of breast cancer in high-risk post-menopausal women (IBIS-II): an international, double-blind, randomized placebo-controlled trial. *Lancet, 383*:1041–1048. Doi: 10.1016/S0140-6736(13)62292-8

Euhus, D.M., & Diaz, J. (2014). Breast Cancer Prevention. *The Breast Journal*, *21*(1),76-81. Doi.10.1111/tbj.12353

Goss, P.E., Ingle, J.N., Ales-Martinez, J.E., Cheung, A.M., Chlebowski, R.T., Wactawski-Wende, J, …Richardson, H. NCIC CTG MAP.3 Study Investigators. (2011). Exemestane for breast-cancer prevention in post-menopausal women. *New England Journal of Medicine, 64*, 2381–2391. doi: 10.1056/NEJMoa1103507

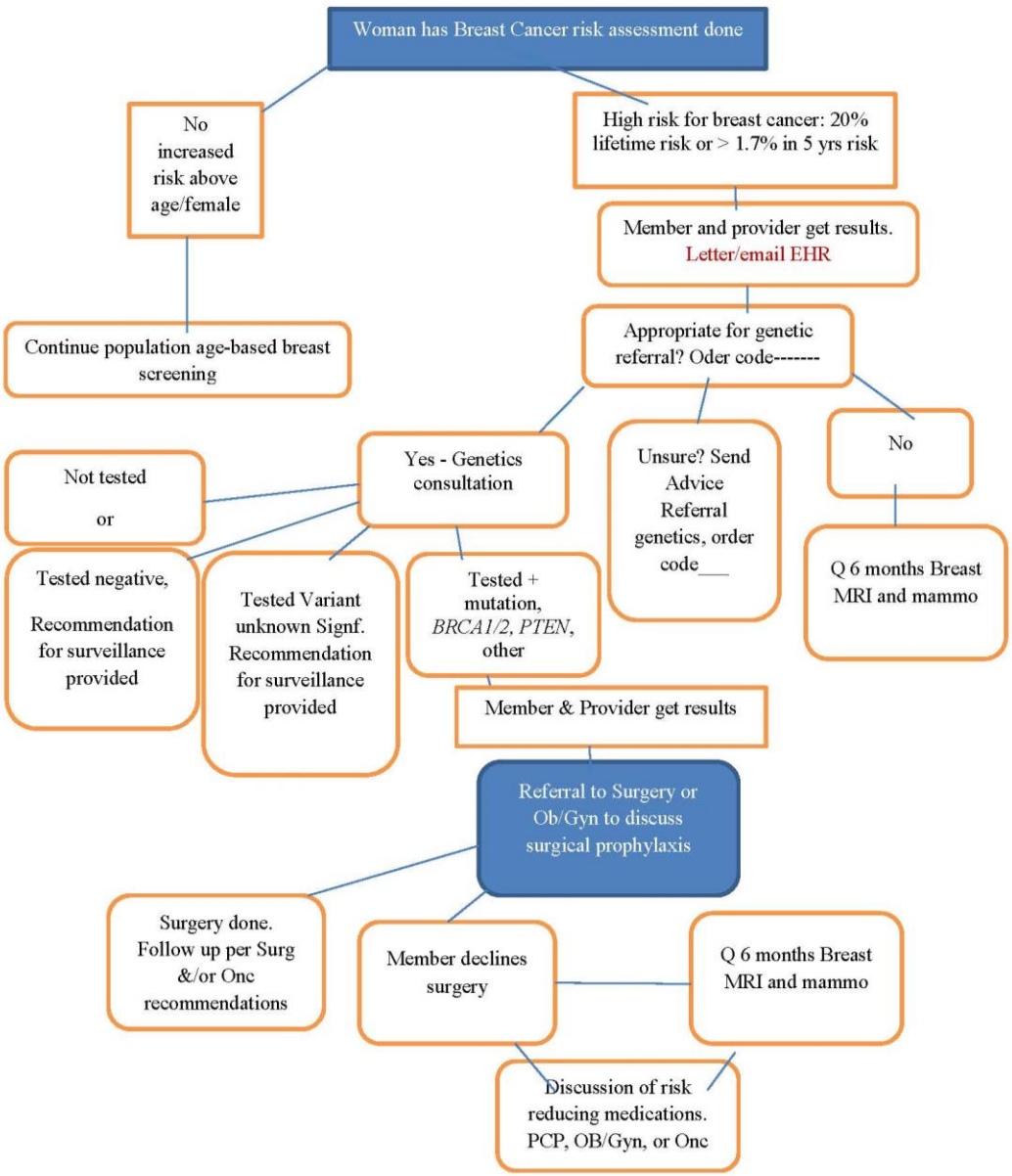
Holmberg, C., Waters, E.A., Whitehouse, K., Daly, M.,& McCaskill-Stevens, W. (2015). My lived experiences are more important than your probabilities: The role of individualized risk estimates for decision making about participation in the Study of Tamoxifen and Raloxifene (STAR). *Medical Decision Making, 35,* 1010-1022, doi:10.1177/0272989X15594382

Mocellin, S. (2016). Risk-reducing medication for primary breast cancer: a network meta-analysis. *Cochrane Database of Systematic Reviews*, (5), doi:10.1002/14651858.CD012191

Visvanathan, K., Hurley, P., Bantug, E. Brown, P., Col, N.,F., Cuzick, J.…Lippman, S.M. ASCO. (2013, August 10). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology*

Vogel, Costantino, Wickerham et al. (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP **Study of Tamoxifen and Raloxifene (STAR)** P-2 trial. *JAMA, 295,* 2727–2741.

Algorithm



APPENDIX H

AMERICAN ASSOCIATION OF COLLEGES OF NURSING'S ESSENTIALS OF DOCTORAL EDUCATION FOR ADVANCED NURSING PRACTICE

American Association of Colleges of Nursing
The Essentials of Doctoral Education
for Advanced Nursing Practice
October 2006

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