

Identification and prioritization of candidate genes for symptom variability in breast cancer survivors based on disease characteristics at the cellular level

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Abstract: Research is beginning to suggest that the presence and/or severity of symptoms reported by breast cancer survivors may be associated with disease-related factors of cancer. In this article, we present a novel approach to the identification and prioritization of biologically plausible candidate genes to investigate relationships between genomic variation and symptom variability in breast cancer survivors. Cognitive dysfunction is utilized as a representative breast cancer survivor symptom to elucidate the conceptualization of and justification for our cellular, disease-based approach to address symptom variability in cancer survivors. Initial candidate gene identification was based on genes evaluated as part of multigene expression profiles for breast cancer, which are commonly used in the clinical setting to characterize the biology of cancer cells for the purpose of describing overall tumor aggressiveness, prognostication, and individualization of therapy. A list of genes evaluated within five multigene expression profiles for breast cancer was compiled. In order to prioritize candidate genes for investigation, genes used in each profile were compared for duplication. Twenty-one genes (*BAG1*, *BCL2*, *BIRC5*, *CCNB1*, *CENPA*, *CMC2*, *DIAPH3*, *ERBB2*, *ESR1*, *GRB7*, *MELK*, *MKI67*, *MMP11*, *MYBL2*, *NDC80*, *ORC6*, *PGR*, *RACGAP1*, *RFC4*, *RRM2*, and *SCUBE2*) are utilized in two or more profiles, including five genes (*CCNB1*, *CENPA*, *MELK*, *MYBL2*, and *ORC6*) used in three profiles. To ensure that the parsimonious 21 gene set is representative of the more global biological hallmarks of cancer, an Ingenuity Pathway Analysis was conducted. Evaluation of genes known to impact pathways involved with cancer development and progression provide a means to evaluate the overlap between the biological underpinnings of cancer and symptom development within the context of cancer.

Keywords: breast neoplasms, biological markers, genes, signs and symptoms, cognition

Introduction

Many cancer survivors experience a variety of disruptive and burdensome symptoms, including fatigue, pain, altered sleep, mood dysregulation, and cognitive dysfunction long into survivorship.¹⁻³ Although our ability to describe the duration, frequency, and severity of symptoms related to cancer and cancer treatments has vastly improved, our understanding of the mechanisms that influence symptom variability and our ability to personalize symptom prediction for an individual cancer survivor and intervene effectively remain limited. While still in its infancy, research is beginning to suggest that the presence and/or severity of symptoms reported by cancer survivors may not be solely the result of cancer treatments, but may be associated with disease-related

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factors of cancer and/or host characteristics that predispose an individual to cancer as well as a particular symptom.⁴⁻⁶

Breast cancer survivors have been the focus of a large proportion of cancer survivor symptom research. Studies conducted with breast cancer survivors on the symptom of cognitive dysfunction especially, are contributing an increasing amount of evidence in support of our hypothesis that disease-related factors of cancer and/or host characteristics that influence cancer development or progression contribute to the presence and severity of symptoms experienced by cancer survivors.

Cognitive dysfunction research in breast cancer survivors has traditionally concentrated on the direct neurotoxic effect of chemotherapeutic agents on the brain. Often referred to as “chemo brain” or “chemo fog”, short- and long-term cognitive changes have been well-documented in women with breast cancer receiving chemotherapy.⁷ With the increasing use of antiestrogen therapies for prevention of breast cancer recurrence, the influence of estrogen and the use of antiestrogen therapies on cognitive decline in breast cancer survivors have become an additional focus of research on treatment-related cognitive changes.⁸⁻¹⁴

However, more recent research demonstrates that cognitive changes may actually occur in breast cancer survivors prior to initiation of adjuvant chemotherapy and/or antiestrogen therapy. In a study of 109 women with breast cancer scheduled to receive chemotherapy, Hermelink et al¹⁵ found that group mean scores were significantly poorer than test norms on five out of twelve cognitive tests before the start of treatment. In addition, 33 survivors scored in the lower fifth percentile of test norms on two or more cognitive tests unrelated to depression, anxiety, or self-reported cognitive problems. Similarly, Wefel et al¹⁶ reported that 29 out of 84 breast cancer survivors diagnosed with stage 1–3a breast cancer were classified as cognitively impaired (ie, multiple cognitive tests with z -scores ≤ -1.5 or a single test with z -score ≤ -2.0) before receiving chemotherapy compared to normative data.

Even more compelling are findings from studies comparing the cognitive function of breast cancer survivors to healthy controls. Ahles et al¹⁷ found that women with invasive breast cancer had poorer overall cognitive performance compared to women with noninvasive breast cancer and healthy controls. Bender et al¹⁸ also reported pretreatment differences in cognitive function in the domains of verbal learning and memory and attention between women with breast cancer prescribed antiestrogen therapy with or without chemotherapy and healthy controls matched on age and years of education. Although not statistically significant, Schagen

et al¹⁹ found that 16.4% of survivors prescribed chemotherapy and 29.8% of survivors with stage 1 breast cancer who were prescribed no systemic treatment displayed cognitive impairment before initiation of adjuvant treatment compared to 10% of healthy controls.

While multiple factors potentially predict cognitive function in women with breast cancer prior to adjuvant therapy, we hypothesize that these pretreatment findings suggest that disease-related factors inherent in breast cancer and/or host characteristics that predispose an individual to cancer as well as cognitive dysfunction may be a major determinant of cognitive changes in women with breast cancer. Additionally, only a subset of breast cancer survivors appears to be affected by cognitive dysfunction. We further hypothesize that heterogeneity in the biology of breast cancers at the cellular level could account for a significant proportion of reported discrepancies in cognitive function among survivors.

One common clinical tool used to evaluate the underlying biology of breast cancer cells is the prognostic multigene expression profile for breast cancer. These profiles enhance knowledge received from traditional tumor features and utilize predictive algorithms of tumor gene expression levels to individualize treatment through estimation of adjuvant therapy benefit and distant cancer recurrence risk. Thus, each prognostic multigene expression profile is comprised of genes that play an important role in breast cancer aggressiveness and progression, and, consequently, represent ideal candidates for a genetic association study exploring our hypotheses (Figure 1).

In this article, we specifically aim to present a novel approach, based on genes examined in prognostic multigene expression profiles for breast cancer, to the identification and prioritization of biologically plausible candidate genes for future investigations of the association between genetic variation and

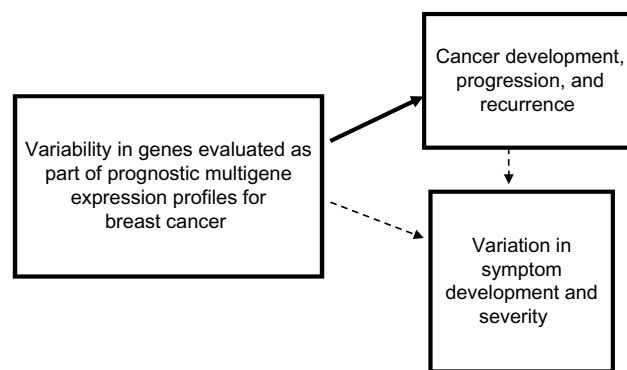


Figure 1 Conceptual model of using variability in genes evaluated as part of prognostic multigene expression profiles for breast cancer to test the hypothesis that heterogeneity in the biology of breast cancers at the cellular level could account for symptom variation.

Note: Dashed arrows represent relationships to be tested in future investigations.

Table 1 Prognostic multigene expression profiles

Profile	Provider	Number of cancer genes evaluated	Clinical utility	Patient eligibility	Website	Reference
11-gene expression signature	Breast Cancer Index SM bioTheranostics, Inc. (San Diego, CA, USA)	7 (5 gene molecular grade index; 2 gene HOXB13; IL17BR index, an expression ratio biomarker)	Predicts late (5–10 year) and overall (0–10 year) recurrence risk as well as likelihood of endocrine therapy benefit; stratifies patients into high or low risk of distant recurrence and high or low likelihood of benefit from extended endocrine therapy	Patients with ER (+), lymph node (-/+), 1–3 positive nodes), early stage breast cancer who are distant recurrence-free	http://breastcancerindex.com	20–22
14-gene prognostic expression signature	Not currently supported	14	Predicts distant metastasis; guides treatment decisions related to adjuvant therapy	Patients with ER (+), lymph node (-), early stage breast cancer	NA	23
21-gene breast cancer assay	Oncotype DX [®] Genomic Health [®] , Inc. (Redwood City, CA, USA)	16 (for invasive breast cancer) 7 (for DCIS)	Predicts 10-year risk of distant recurrence and likelihood of chemotherapy benefit for invasive breast cancer; gene expression levels are aggregated and provided as a scaled Recurrence Score [®] result (on a 0–100 scale); patients are stratified into high, intermediate, or low risk groups; also provides quantitative single gene scores for ER, PR, and HER2; predicts 10-year risk of distant recurrence (DCIS or invasive) for DCIS	Pre- or post-menopausal patients with ER (+), lymph node (-), HER2 (-), stage I, II or IIIa invasive breast cancer Post-menopausal patients with lymph node (+, 1–3 positive nodes), HR (+), HER2 (-), stage I, II or IIIa invasive breast cancer	http://breast-cancer.oncotypedx.com	24,25
50-gene breast cancer prognostic gene signature assay	Prosigna [®] NanoString [®] Technologies, Inc. (Seattle, WA, USA)	50	Predicts 10-year distant recurrence-free survival using gene-algorithm generated Prosigna [®] Score (0–100); stratifies patients into high, intermediate, or low risk groups. Provides risk group classification to facilitate interpretation of Prosigna [®] score with clinical outcomes	DCIS treated by lumpectomy, not mastectomy, regardless of Tamoxifen status (+/-) Post-menopausal patients with HR (+), lymph node (-), stage I or II invasive breast cancer to be treated with adjuvant endocrine therapy alone Post-menopausal patients with HR (+), lymph node (+, 1–3 positive nodes), stage II invasive breast cancer treated with adjuvant endocrine therapy alone	http://www.prosigna.com	26
70-gene breast cancer recurrence assay	MammaPrint [®] Agendia [®] (Irvine, CA, USA)	70	Predicts 5- and 10-year distant recurrence and guides treatment decisions, including potential chemotherapy benefit; stratifies patients into low or high risk groups	Patients with ER (+/-), lymph node (-), stage I or II invasive breast cancer tumor ≤5 cm in size	http://www.agendia.com/healthcare-professionals/breast-cancer/mammaprint	27

Notes: Information regarding Prosigna[®] is provided courtesy of NanoString Technologies, Inc., www.Prosigna.com. © 2014–15 NanoString Technologies, Inc. All rights reserved. Information regarding Oncotype DX[®] is provided courtesy of Genomic Health, Inc., www.genomichealth.com. © 2015 Genomic Health, Inc. All rights reserved.

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor.

symptoms experienced by breast cancer survivors. We will focus on 1) characteristics of five different prognostic multigene expression profiles for breast cancer, 2) prioritization of candidate genes replicated in two or more profiles, 3) biological functions of our identified, parsimonious candidate gene set, and 4) a discussion of the potential expanded clinical utility of prognostic multigene expression profiles for breast cancer, and, more generally, cancer symptom prediction.

Methods

Selected breast-cancer-related prognostic multigene expression profiles

Prognostic multigene expression profiles use tumor gene expression levels to evaluate the underlying biology of breast cancer cells and predict long-term outcomes and potential benefit of additional adjuvant therapy. Several groups have developed prognostic multigene expression profiles for breast cancer: the eleven-gene expression signature (marketed as the Breast Cancer IndexSM by bioTheragnostics, Inc., San

Diego, CA, USA),²⁸ the 14-gene prognostic expression signature (described in Tutt et al²³), the 21-gene breast cancer assay (marketed as the Oncotype DX[®] Breast Cancer Assay by Genomic Health[®], Inc., Redwood City, CA, USA),^{29,30} the 50-gene breast cancer prognostic gene signature assay (marketed as the Prosigna[®] Breast Cancer Prognostic Gene Signature Assay by NanoString[®] Technologies, Inc., Seattle, WA, USA) based on the PAM50 Breast Cancer Intrinsic Classifier,³¹ and the 70-gene breast cancer recurrence assay (marketed as the MammaPrint[®] 70 Gene Breast Cancer Recurrence Assay by Agendia[®], Irvine, CA, USA).^{32,33}

The number of cancer genes utilized in each profile varies greatly, ranging from 7 in the eleven-gene expression signature to 70 in the 70-gene breast cancer recurrence assay. All of the prognostic multigene expression profiles provide predictions of 5- and/or 10-year distant breast cancer recurrence risk, except the 14-gene prognostic expression signature, which is specifically intended for prediction of distant metastasis. With the exception of the 50-gene breast cancer prognostic gene

Table 2 Genes utilized in two or more prognostic multigene expression profiles as indicated by X

Gene	11-gene expression profile	14-gene prognostic expression signature	21-gene breast cancer assay	50-gene breast cancer prognostic gene signature assay	70-gene breast cancer recurrence assay	Gene function
<i>BAG1</i>			X	X		Enhances antiapoptotic effect of BCL2
<i>BCL2</i>			X	X		Blocks the apoptotic death of certain cells
<i>BIRC5</i>			X	X		Encodes regulatory proteins that prevent apoptosis
<i>CCNB1</i> ^a		X	X	X		Encodes a regulatory protein involved in mitosis
<i>CENPA</i> ^a	X	X			X	Encodes for a centromere protein; histone H3 variant
<i>CMC2</i>		X			X	Potential involvement in mitochondrial cytochrome c oxidase biogenesis ³⁴
<i>DIAPH3</i>		X			X	Involved in actin remodeling and regulation of cell movement and adhesion
<i>ERBB2</i>			X	X		Encodes HER2, an epidermal growth factor receptor protein
<i>ESR1</i>			X	X		Encodes an estrogen receptor
<i>GRB7</i>			X	X		Encodes a growth factor receptor-binding protein
<i>MELK</i> ^a		X		X	X	Involved in cell cycle regulation, apoptosis, and splicing regulation ³⁵⁻³⁷
<i>MKI67</i>			X	X		Involved in cellular proliferation
<i>MMP11</i>			X	X		Involved in extracellular matrix breakdown
<i>MYBL2</i> ^a		X	X	X		Encodes a nuclear protein; involved in cell cycle progression
<i>NDC80</i>				X	X	Organization and stabilization of microtubule-kinetochore attachments
<i>ORC6</i> ^a		X		X	X	Involved in chromosome replication and segregation
<i>PGR</i>			X	X		Encodes a progesterone receptor; mediates effects of progesterone
<i>RACGAP1</i>	X	X				Involved in cytokinesis initiation and control of cellular growth
<i>RFC4</i>		X			X	Required for elongation of primed DNA templates
<i>RRM2</i>	X		X			Catalyzes the formation of deoxyribonucleotides from ribonucleotides
<i>SCUBE2</i>			X		X	Potential breast tumor suppressor gene ³⁸

Notes: Information on gene function was obtained from the NCBI's Gene Database³⁹ unless noted otherwise. ^aIndicates a gene used in three expression profiles.

Abbreviation: NCBI, National Center for Biotechnology Information.

signature assay, which is not purposed to assist in the selection of optimal therapy, results from the remaining prognostic multigene expression profiles are intended to guide clinical treatment decisions, relaying the benefit of additional adjuvant chemotherapy and/or antiestrogen therapy. Table 1 compares important characteristics of the five prognostic multigene expression profiles, including number of genes evaluated, clinical utility, and patient eligibility.

Identification and prioritization of candidate genes

A list of genes evaluated within each of the five prognostic multigene expression profiles was compiled. Lists of genes were obtained from the following locations in March 2014: the eleven-gene expression profile (Jerevall et al),²⁸ the 14-gene prognostic expression signature (Tutt et al),²³ the 21-gene breast cancer assay (<http://breast-cancer.oncotypedx.com>),

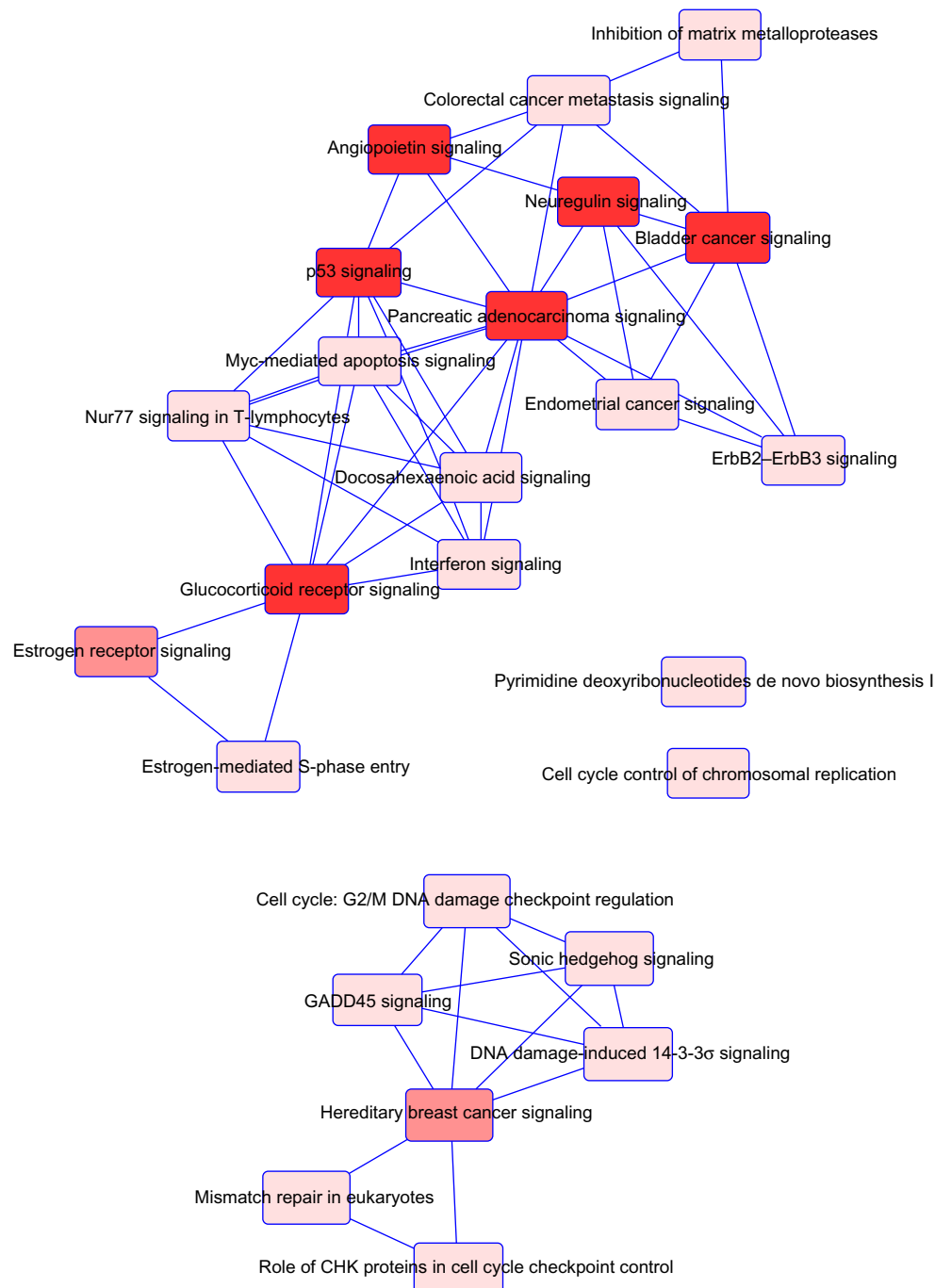


Figure 2 Overlapping canonical pathways map representing shared biology among the identified candidate genes.

Notes: Connected canonical pathways share one or more genes in common. The brighter the red of the node, the more significant the canonical pathway in the gene set. The canonical pathways map was generated through the use of QIAGEN's Ingenuity Pathway Analysis (IPA[®], QIAGEN Redwood City, www.qiagen.com/ingenuity).

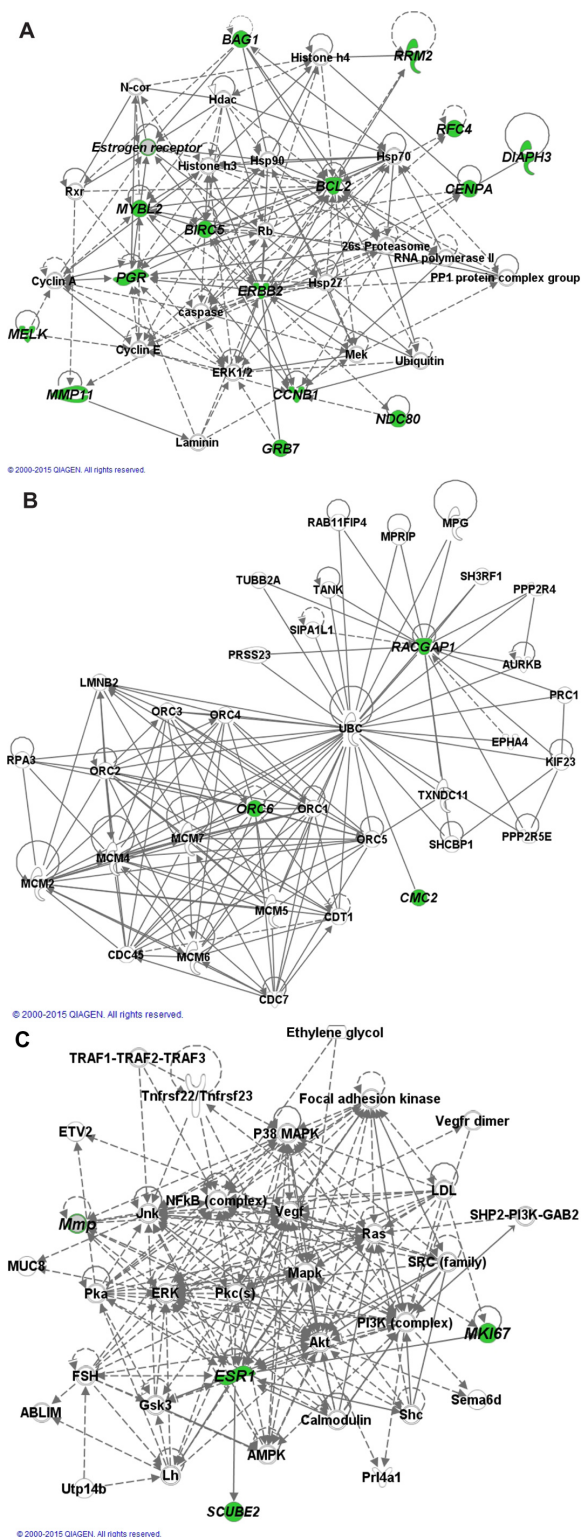


Figure 3 Gene-gene networks generated by pathway analysis.

Notes: The networks were generated through the use of QIAGEN's Ingenuity Pathway Analysis (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity). Identified candidate genes are highlighted in green. All identified candidate genes are included. The main associated functions of each network are as follows: (A) cancer, organismal injury and abnormalities, and reproductive system disease; (B) DNA replication, recombination, and repair, connective tissue disorders, and dental disease; and (C) cellular development, reproductive system development and function, and molecular transport. The node shapes and relationship type legend can be found at http://ingenuity.force.com/ipa/articles/Feature_Description/Legend.

the 50-gene breast cancer prognostic gene signature assay (<https://genome.unc.edu/pubsup/breastGEO/>), and 70-gene breast cancer recurrence assay (Tian et al).⁴⁰ Genes utilized in two or more profiles were prioritized for selection.

Pathway analysis of gene set

In order to ensure adequate representation of the biological capabilities of cancer in the parsimonious high priority candidate gene set, a gene-gene pathway analysis was conducted, using QIAGEN's Ingenuity® Pathway Analysis software (IPA®, QIAGEN Redwood City, CA, USA, www.qiagen.com/ingenuity), to evaluate functional networks. Both direct and indirect relationships were analyzed. All molecules and/or relationships were considered.

Results

Among the five included prognostic gene expression profiles, 127 unique genes were identified. Twenty-one genes (*BAG1*, *BCL2*, *BIRC5*, *CCNB1*, *CENPA*, *CMC2*, *DIAPH3*, *ERBB2*, *ESR1*, *GRB7*, *MELK*, *MKI67*, *MMP11*, *MYBL2*, *NDC80*, *ORC6*, *PGR*, *RACGAP1*, *RFC4*, *RRM2*, and *SCUBE2*) are utilized in two or more of the profiles (Table 2). Five genes (*CCNB1*, *CENPA*, *MELK*, *MYBL2*, and *ORC6*) are used in three profiles. Primary functions of the identified candidate genes are provided in Table 2.

The pathway analysis revealed that the main molecular and cellular functions of the parsimonious, high priority gene set are cell cycle, cellular development, cellular growth and proliferation, cell death and survival, and gene expression. Canonical pathways containing one or more of the identified 21 genes are displayed in Figure 2. Three unique networks were identified (Figure 3). The main associated diseases and functions of the three networks are 1) cancer, organismal injury and abnormalities, and reproductive system disease; 2) DNA replication, recombination, and repair, connective tissue disorders, and dental disease; and 3) cellular development, reproductive system development and function, and molecular transport. The pathway analysis also identified a number of plausible upstream transcription regulators of the identified 21 gene set, including *TP53*, *CDKN1A*, *CDKN2A*, *E2F1*, and *E2F4*.

Discussion and conclusion

In the future, we envision a holistic, personalized health care environment, in which breast cancer survivors receive not only a refined cancer diagnosis and prognosis based on the results of prognostic multigene expression profiles, but genetically tailored preclinical symptom prediction and

proactive symptom management as well. Inspired by findings related to reported changes in cognitive function in women with breast cancer, this project, intended to identify and prioritize biologically plausible candidate genes, represents an initial and integral step in establishing a relationship between genetic variation and symptom variability in breast cancer survivors.

Driven by our hypothesis that symptom variability in breast cancer survivors is related to variation in the biology of cancer cells, we employed the innovative approach detailed in this article to select candidate genes based on prognostic multigene expression profiles for breast cancer. While we believe that all 127 unique genes evaluated as part of the included prognostic multigene expression profiles for breast cancer should be considered as candidates to test the proposed hypothesis, our project revealed considerable overlap in genes represented in the profiles with 21 genes replicated in two or more profiles. Five of the 21 replicated genes are used in three profiles. Because each prognostic multigene expression profile was developed to individualize breast cancer prognostication based on associations between breast cancer tumor gene expression levels and clinically relevant cancer outcomes, including recurrence and metastasis, replication of genes utilized in multiple profiles may be particularly important in describing the heterogeneity of breast cancer tumor cell biology and, consequently, should be prioritized for evaluation.

Nevertheless, by limiting a future investigation to variation in genes replicated in two or more profiles, we risk the inadvertent elimination of one or more of the biologic capabilities that enable tumor growth and metastatic dissemination. Eight biologic hallmarks of cancer have been identified and include resisting cell death, deregulating cellular energetics, sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, activating invasion and metastasis, and inducing angiogenesis.⁴¹ To ensure that our parsimonious, high priority gene set broadly incorporated these eight hallmarks, an Ingenuity[®] Pathway Analysis was conducted. The results of our pathway analysis revealed that the main molecular and cellular functions of the gene set were cell cycle, cellular development, cellular growth and proliferation, cell death and survival, and gene expression. We also found that the majority of the canonical pathways the genes in our identified gene set are contained within are related to cancer/cellular signaling. Furthermore, the genes identified by the analysis as potential upstream regulators of the gene set, *TP53*, *CDKN1A*, *CDKN2A*, *E2F1*, and *E2F4*, all play important roles in cell cycle control and tumor suppression. Due to the overlap between the molecular

and cellular functions of the gene set and the hallmarks of cancer, we believe that the biologic hallmarks of cancer are represented in the prioritized gene set.

Interestingly, a further examination of genes, molecules, gene products, and gene complexes/interactions in the identified networks revealed minimal overlap with genes in the prognostic multigene expression profiles. We were surprised to find that only six genes (*CCNE1*, *CCNE2*, *FLT1*, *MCM6*, *MMP9*, and *PRC1*), beyond those contained in the inputted 21 gene set, are utilized in one of the five included prognostic multigene expression profiles. While unintentional and not the purpose of this project, we believe that the remaining network genes could be considered as potential candidates to develop new prognostic multigene expression profiles for breast cancer, to increase the sensitivity/specificity of current profiles, and/or as a means to potentially expand patient eligibility criteria.

Although conceptualized within the context of cognitive dysfunction, the identified genes would be ideal candidates for investigations of symptom variability in other disruptive and burdensome symptoms associated with breast cancer, its treatments, or both as well. The identified 21 gene set would be especially relevant for symptoms previously found to be associated with disease-related factor of breast cancer, such as fatigue, which has been predicted by tumor size and lymph involvement.^{42,43} Moreover, the novel approach we employed to select candidate genes for investigations of variability in breast cancer symptoms can also be applied to other cancers that have biologically based commercially available prognostic multigene expression profiles, such as colon and prostate cancer, and associated symptoms.

Genetic variability within the proposed candidate gene set can be evaluated in a number of ways, including evaluation of polymorphisms, gene expression levels, protein levels, and epigenetic changes in both the host and tumor tissue. We recognize that symptom variability, especially at the time of diagnosis, may be driven by tumor gene expression, the consequences of tumor expression and related protein production on the rest of the body, and subsequent removal and treatment of the primary tumor and secondary sites. Thus, we recommend that future symptomatology studies focus on relationships between tumor gene expression/protein levels and symptom variability in cancer survivors. Significant results from tumor gene expression studies in particular, could greatly and directly expand the clinical utility of currently available prognostic multigene expression profiles. For instance, a modified version of the gene expression algorithms could potentially generate a range of Cognitive Decline Risk Scores or Fatigue Risk Scores,

based on the treatment regimen that is ultimately selected, other clinicopathologic tumor features, and baseline patient characteristics for each breast cancer survivor. However, relationships between host DNA and symptom variability are desirable as well because host DNA variation remains constant over time and is not tissue specific. Prediction of symptoms using host DNA would be especially advantageous for unusable tumor tissue, survivors with a clear prognosis and treatment regimen recommendation based on other clinicopathologic tumor features who would not be eligible for further prognostic multigene expression profile testing, or post hoc symptom prediction after tissue RNA has degraded and quantified gene expression level accuracy would be questionable.

However, we would like to acknowledge that this approach is not without limitations. Of particular interest, the multigene expression profiles from which candidate genes were selected, with the exception of the 70-gene breast cancer recurrence assay, all require positive breast cancer tumor estrogen or progesterone receptor status as an eligibility criterion. Consequently, genetic variation important for symptom variability in women with hormone receptor negative and triple-negative breast cancers may not be adequately captured in the prioritized gene set. In other words, the clinical applicability of breast cancer survivor symptom prediction may be limited to women with tumors that reflect the eligibility criteria of the five multigene expression profiles used to generate the candidate gene list. Additional candidate genes should be considered for other subsets of breast cancers not emphasized in the currently available multigene expression profiles.

Undoubtedly, the results of future investigations of symptom variability in breast cancer survivors based on disease characteristics at the cellular level, such as genetic variability in the high priority 21 gene set identified in this article, have the potential to substantially impact both the care of breast cancer survivors and the practice of health care providers alike, extending the clinical utility of prognostic multigene expression profiles for breast cancer and providing the patient and the provider with a means of weighing not only cancer prognosis and recurrence, but also the quality of life due to burdensome symptoms, into treatment decisions as well.

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Disclosure

The authors report no conflicts of interest in this work.

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