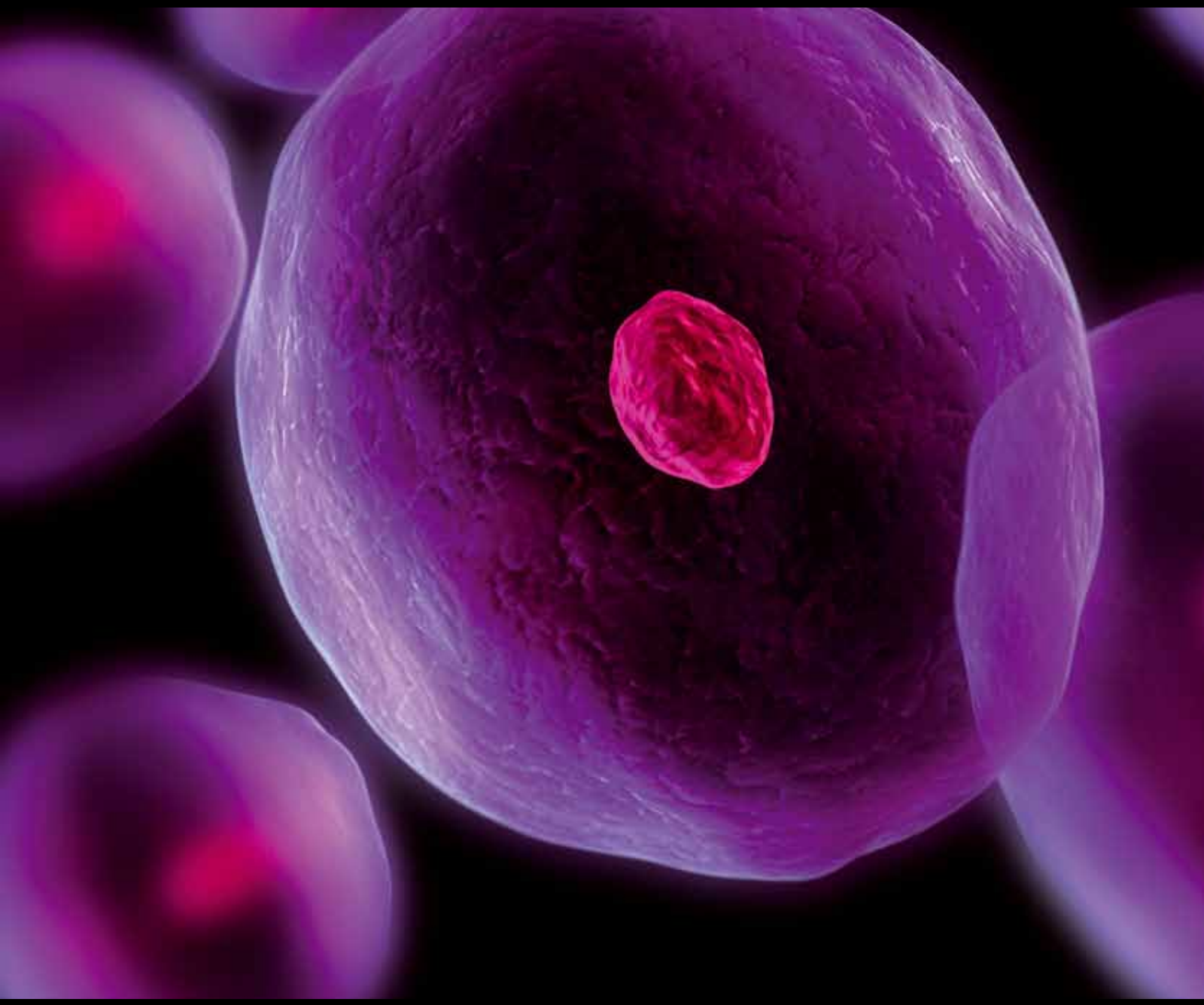
Journal of Cancer Epidemiology

The Front Line of Genomic Translation

Guest Editors: Suzanne C. O'Neill, Colleen M. McBride, Angela D. Bryan, Laura M. Koehly, and Louise Wideroff



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Editorial Board

Contents

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Editorial

The Front Line of Genomic Translation

Suzanne C. O'Neill,[1] Colleen M. McBride,[2] Angela D. Bryan,[3] Laura M. Koehly,[2] and Louise Wideroff[4]

[1] *Lombardi Comprehensive Cancer Center, Medical Center, Georgetown University, Washington, DC 20007, USA*
[2] *Social and Behavioral Research Branch, National Human Genome Research Institute, NIH, MD 20892, USA*
[3] *Department of Psychology, University of Colorado, CO 80309, USA*
[4] *Division of Basic Neuroscience and Behavioral Research, National Institute on Drug Abuse, NIH, MD 20892, USA*

Correspondence should be addressed to Suzanne C. O'Neill, sco4@georgetown.edu

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Cancer prevention, detection, and treatment represent the frontline of genomic translation. Increasingly, new genomic knowledge is being used to inform personalized cancer prevention recommendations and treatment [1–3]. Genomic applications proposed and realized span the full cancer continuum, from cancer prevention and early detection vis a vis genomic risk profiles to motivate behavioral risk reduction and adherence [4] to screening and prophylactic prevention recommendations for high-risk families [5–7], to enhancing cancer survivorship by using genomic tumor profiles to inform treatment decisions and targeted cancer therapies [8, 9]. Yet the utility for many of these applications is as yet unclear and will be influenced heavily by the public's, patients', and health care providers' responses and innumerous other factors, such as health care delivery models [3]. The contributors to this special issue consider various target groups' responses and contextual factors. To reflect the cancer continuum, the special issue is divided into three broad, overlapping themes—primary prevention, high risk families and family communication and clinical translation.

The issue begins with three papers that consider applications of genomic information to promote the primary prevention of cancer. Hay and colleagues present results of a randomized trial evaluating prototypic genetic risk feedback with first degree relatives of patients with melanoma. Using an experimental pre-post design, the authors tested whether varied feedback type (high risk mutation, gene-environment, nongenetic) and risk level (positive versus negative findings), all emphasizing the importance of family history regardless of feedback type, influenced families' risk perceptions, and behavioral intentions. Findings indicated that risk level, but not feedback type, was associated with higher perceived risk and behavioral intentions for sun protection and skin screening. It is widely acknowledged that efforts should be directed to building an evidence base to inform genomic risk communication practice. This will be essential as new technologies such as whole genome sequencing begin to yield voluminous amounts of risk information for providers, patients and their families. Thus unpacking the essential elements of effective risk communications could facilitate translation of emerging and increasingly complex genomic risk information.

Rutten and colleagues used data from the 2008 and 2011 waves of the Health Information National Trends Survey (HINTS), a nationally representative sample, to assess the public's awareness of direct to consumer (DTC) genetic testing. As expected, awareness of DTC genetic testing increased significantly (from 29.3% to 36.9%) from 2008 to 2011. Awareness was higher in older adults who had more educational attainment, lived in urban settings, and who already have access to primary care. Awareness also was higher among those with a prior cancer diagnosis, 47.4% versus 35.9% of those without. Thus, affluent and highly educated individuals, as well as those affected by cancer, may be more aggressive information seekers about genetic tests. While DTC access to genetic testing is still highly controversial, these results suggest that such access does not have broad reach and thus may exacerbate existing health disparities.

Finally, in an effort to explore the underlying genetic contribution to exercise behavior, Karoly and colleagues explore associations between biologically plausible single nucleotide

polymorphisms (SNPs) and response to exercise. Their results showed that SNPs in the *FTO*, *CREB1*, and *OPRM1* genes as well as SNPs in *SLIT2* and *FAM5C* were associated with physiological changes and subjective experiences during a session of moderate intensity exercise. Studies like this lay the groundwork for the eventual discovery of large panels of genetic markers that might help health promotion researchers to individually tailor behavioral interventions in ways that could optimize exercise adherence and ultimately decrease cancer incidence.

The second set of papers consider whether genomic risk assessments, including family health history assessments related to and genetic testing for hereditary cancer syndromes, have the potential to inform personalization of disease prevention and treatment behaviors. In order for this personalization to take place, patients must be proactive in informing their providers and their at-risk relatives about inherited disease risk, highlighting the importance of effective communication. Anderson and colleagues examine facilitators and barriers associated with young breast cancer survivors' use of genetics services, as early onset is an indicator of increased likelihood of carrying a mutation. One of the primary barriers to use genetic services was not having been referred to genetics education and risk evaluation by a cancer care provider. Vadaparampil and colleagues focused their attention on communication of test results among newly diagnosed women who were tested. While these survivors typically shared their *BRCA1/2* results with their first-degree female relatives and their medical oncologists, communication was less likely to occur with male relatives or with physicians in other specialties, even their primary care providers. This again highlights multiple opportunities to foster communication within and outside the family. This need does not apply only to those affected with hereditary breast and ovarian cancer, as James and colleagues report that at least 20% of relatives at high risk of familial adenomatous polyposis (FAP) had not discussed their family history with a doctor or had a doctor explain their personal risk of cancer. Taken together, it is clear that reciprocal exchange of information, both within families and between families and their healthcare providers, is necessary for personalization of prevention recommendations and treatments to be realized. Thus, these papers point to the need for evaluating clinic-friendly approaches to expand reciprocal risk communication among patients, family members and providers.

The issue concludes with three papers that consider genomic tools in the oncology clinic. Specifically, within the past decade, gene-expression profiling and pharmacogenetic testing have become an integral part of clinical care for certain types of cancer. Onco*type* DX, a 21-gene expression test performed on tumor tissue, has been used since 2004 to predict metastatic recurrence of early stage, estrogen receptor-positive breast cancer. Patients with elevated recurrence scores, indicative of more aggressive tumors, may opt for adjuvant chemotherapy as part of their treatment plan. In the immediate postmarketing period while awaiting further clinical trial results, some insurers considered the intermediate endpoint of clinical utility (i.e., whether testing has changed the course of treatment) to determine coverage [10]. While data have shown that patients with high recurrence scores tend to receive chemotherapy, the situation is not so clear for the 25% of tested patients with intermediate scores. In this special issue, Malo et al. report on a chart review of patients in an NCI-supported comprehensive cancer center who received Onco*type* DX in 2004–2009. While the data should be interpreted in the context of a small, single site study, after adjustment for a clinical and sociodemographic variables, both high and intermediate recurrence score remained significantly associated with chemotherapy uptake. In turn, Sulayman and colleagues address the psychosocial aspects of Onco*type* DX testing, focusing on the joint effects of recurrence score and treatment decision style. They find that passive decision style was associated with higher distress and lower quality of life, particularly among patients with intermediate recurrence scores. Past patient-reported outcomes research on predictive genetic tests for *BRCA1/2* mutations have enabled genetic counselors and physicians to better integrate counseling into care, thus these results too could result in improved quality of life for carriers and family members [11]. The issue concludes with Cox et al.'s presentation of data from a survey of Oregon health providers' use and knowledge of gene-based predictive and diagnostic tests, as well as pharmacogenetic tests for drug response. Not surprisingly, clinicians reported greater familiarity with tests for which practice guidelines are available, such as tests for breast/ovarian and Lynch syndromes. Although knowledge and test use differed by specialty, many reported limited knowledge of medical genetics and gave lack of familiarity with particular tests as the main reason for not using them in practice. This lag time between commercialization of various genetic tests and widespread adoption in practice presents challenges for effective translation. Accelerated clinical research is needed to inform new practice guidelines as are systematic efforts to build clinicians' competencies in this area.

The articles in this special issue represent a wide range of populations, settings, and contexts.

Acknowledgment

We thank the contributing authors and the anonymous reviewers who made this special issue possible. We hope that this issue will stimulate more research at the frontline of translational cancer genomics, behavioral science, clinical care, and public health.

Suzanne C. O'Neill
Colleen M. McBride
Angela D. Bryan
Laura M. Koehly
Louise Wideroff

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Research Article

Patterns of Cancer Genetic Testing: A Randomized Survey of Oregon Clinicians

Summer L. Cox,[1] Amy I. Zlot,[1] Kerry Silvey,[1,2] Debi Elliott,[3] Tara Horn,[3] Amber Johnson,[3] and Richard F. Leman[4]

[1] *Oregon Genetics Program, Public Health Division, Oregon Health Authority, Portland, OR 97232, USA*
[2] *Oregon Center for Children and Youth with Special Health Needs, Child Development and Rehabilitation Center, Oregon Health & Science University, Portland, OR 97239, USA*
[3] *Survey Research Lab, Office of Research and Sponsored Projects, Portland State University, Portland, OR 97201, USA*
[4] *Center for Public Health Practice, Public Health Division, Oregon Health Authority, Portland, OR 97232, USA*

Correspondence should be addressed to Summer L. Cox, summer.l.cox@state.or.us

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Introduction. Appropriate use of genetic tests for population-based cancer screening, diagnosis of inherited cancers, and guidance of cancer treatment can improve health outcomes. We investigated clinicians' use and knowledge of eight breast, ovarian, and colorectal cancer genetic tests. *Methods*. We conducted a randomized survey of 2,191 Oregon providers, asking about their experience with fecal DNA, OncoVue, *BRCA*, *MMR*, *CYP2D6*, tumor gene expression profiling, *UGT1A1*, and *KRAS*. *Results*. Clinicians reported low confidence in their knowledge of medical genetics; most confident were OB-GYNs and specialists. Clinicians were more likely to have ordered/recommended *BRCA* and *MMR* than the other tests, and OB-GYNs were twice as likely to have ordered/recommended *BRCA* testing than primary care providers. Less than 10% of providers ordered/recommended OncoVue, fecal DNA, *CYP2D6*, or *UGT1A1*; less than 30% ordered/recommended tumor gene expression profiles or *KRAS*. The most common reason for not ordering/recommending these tests was lack of familiarity. *Conclusions*. Use of appropriate, evidence-based testing can help reduce incidence and mortality of certain cancers, but these tests need to be better integrated into clinical practice. Continued evaluation of emerging technologies, dissemination of findings, and an increase in provider confidence and knowledge are necessary to achieve this end.

1. Introduction

Genomic medicine has entered the clinical setting. Currently available genomic[1] and genetic tests enable disease surveillance and individually tailored treatment, and many more such tests are on the horizon. Chronic diseases, including breast, ovarian, and colorectal cancer, have multifactorial etiologies, including genetic components. In 2010, breast and colorectal cancer were among the four most commonly diagnosed cancers and were the second and third most common causes of cancer death in both the USA and in Oregon [1]. An estimated 5%–10% of all breast and ovarian cancers are hereditary, meaning a single gene mutation contributed to development of the cancer. The majority of these inherited cancer cases are due to mutations in breast cancer susceptibility genes, which include *BRCA*1 and *BRCA*2 (*BRCA*) [2]. Women within the general population have a 12% lifetime risk of developing breast cancer and a 1% lifetime risk of developing ovarian cancer [3]. For women with *BRCA* mutations, however, the lifetime cancer risk is greater. It is estimated that 47%–66% of women with *BRCA*1 mutations will develop breast cancer by age 70, while 35%–46% of them will develop ovarian cancer by that age [4]. Risk of developing certain other cancers (e.g., pancreatic cancer) also increases markedly. Currently, identified mutations account for 5%-6% of colorectal cancer cases [5]. The general population has a 6% lifetime risk of developing colorectal cancer, but for those with mismatch

repair gene (*MMR*) mutations, the risk increases to 80%, and the risk of developing certain other cancers (e.g., endometrial cancer) also increases substantially [6]. Morbidity from these heritable mutations places a substantial burden on both those who have them and on the health care system.

Genetic tests that can be used for population-based cancer screening, diagnosis of inherited cancer syndromes, and selection of specific cancer therapies most likely to be effective for a given patient are now commercially available [7–15]. In order to take full advantage of valid and clinically useful genetic tests, health care providers must not only become aware of them, but also become knowledgeable about their use and interpretation. Providers must continue to improve their skills in assessing family history and other relevant factors to stratify patient risk for specific cancers, improve decision making for referral to genetic specialists[2], and decide when consideration of genetic testing is appropriate for a given patient [16–23]. The increased use of direct-to-consumer marketing for cancer-related genetic tests makes this doubly important, as clinicians are increasingly called upon to interpret the results of a genetic test that may have been ordered directly by their patient rather than a health care provider.

In the current health care milieu, providers in many different settings can order or recommend a genetic test. Physicians or midlevel providers such as physician assistants and nurse practitioners can order these tests in a primary care setting, alternate or complementary care providers such as naturopaths may order them, and specialists who primarily see patients with cancer may order these tests as well. The familiarity of these different provider groups with such tests, their patterns in ordering them, and their confidence in interpreting them may differ.

Our survey evaluated the extent to which health care providers in different practice settings use eight commercially available genetic tests to assess personal or familial risk for breast, ovarian, and colorectal cancer, or to guide treatment for these conditions. We also explored providers' rationale for ordering/recommending these tests, their reasons for not ordering/recommending these tests if they refrain from doing so, their level of confidence in their knowledge of medical genetics, and whether they refer to genetic specialists. The genetic tests we evaluated fall into three categories: (1) population-based cancer screening, (2) refined risk assessment for specific cancers in patients already identified as high risk due to family or personal history, and (3) testing to guide cancer treatment decisions.

In our study, we surveyed provider use of fecal DNA, OncoVue, *BRCA*, *MMR*, *CYP2D6*, breast cancer tumor gene expression profiling, *UGT1A1*, and *KRAS* testing. Table 1 lists each of the tests, describes them, and summarizes the evidence-based recommendations published by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), the U.S. Preventive Services Task Force (USPSTF), and the National Comprehensive Cancer Network (NCCN). The evidence regarding the clinical utility and potential harms associated with these tests continues to grow. Guidelines for these tests range from recommending use of the test in specific circumstances, to concluding there is insufficient evidence to recommend for or against using the test, to recommending against use of the test. The recommendations conflict for some tests. It is important for clinicians to understand both the benefits and limitations of testing and be aware of the importance of pre- and post-test counseling. A better understanding of how, and why, health care providers use cancer genetic tests can inform policy development and educational efforts to ensure the appropriate and effective use of these tests.

2. Methods

2.1. Study Population. The Oregon Genetics Program conducted the 2010 Oregon Health Care Provider Survey in collaboration with the Portland State University Survey Research Lab. We generated a stratified random sample of primary care providers and specialists practicing in Oregon to evaluate the use of eight genetic tests for breast, ovarian, and colorectal cancer. We used the 2010 licensee databases from the Oregon Medical Board, the Oregon Board of Naturopathic Examiners, and the Oregon State Board of Nursing to identify possible respondents. Because the boards vary in their levels of specificity for practice specialty, in order to survey subspecialists who treat cancer, for example, breast surgeons, we sent surveys to some providers who are unlikely to screen or treat for breast, ovarian, or colorectal cancer, for example, head and neck surgeons. To target our study to providers who screen or treat for breast, ovarian, and colorectal cancer, we asked clinicians whether they recommended screening or treated for breast, ovarian, or colorectal cancer in both a screening postcard and on the survey. We excluded any respondent who reported neither recommending screening nor treating breast, ovarian, or colorectal cancer. We also asked clinicians to self-identify their specialty on the survey and removed surveys from the analysis if the responding clinicians indicated that they did not belong to one of the health care provider groups of interest.

We stratified the potential respondents into four provider groups: primary care providers, naturopaths[3] obstetricians/gynecologists (OB-GYNs), and specialists. Primary Care Providers consisted of family physicians, internal medicine physicians, primary care (general practice, family medicine, or family practice) nurse practitioners, and primary care physician assistants. We analyzed Naturopaths separately to assess patterns of care among this growing class of alternate/complementary care providers. While one might consider obstetrics/gynecology a primary care specialty, we developed a separate stratum for this group because of the frequency with which they evaluate patients for possible ovarian or breast cancer. Specialists consisted of surgeons, colorectal surgeons, general surgeons, gastroenterologists, oncologists, and gynecologic oncologists.

2.2. Survey Instrument. A questionnaire was developed, piloted, and mailed to 2,506 Oregon health care providers in 2010. We sent up to three mailings to recipients. The first mailing included a prenotification letter with endorsements

Table 1: National guidelines for cancer genetic tests included in the 2010 Oregon Health Care Provider Survey.

Test	Description	Recommendation
Population-based screening for specific cancers		
OncoVue	Tests for single nucleotide polymorphisms associated with increased breast cancer risk.	No recommendations from **EGAPP**, **NCCN**, or **USPSTF**.
Fecal DNA	Test designed to screen for colorectal cancer, has better sensitivity than the traditional fecal occult blood test (FOBT), and may be more acceptable to the public than colonoscopy.	(i) **NCCN** considers use of fecal (stool) DNA testing to be an option, but does not recommend it as a "first-line" screening tool [7]. (ii) **USPSTF** found insufficient evidence to recommend use of fecal DNA testing as a screening method for colorectal cancer [14].
Further assessing risk for developing specific cancers in previously identified high-risk populations		
BRCA	Tests designed to detect specific *BRCA* mutations associated with increased risk for breast and ovarian cancers. Providers use results to guide breast and related cancer prevention efforts.	(i) **NCCN** and **USPSTF** recommend *BRCA* testing for patients at increased risk of developing breast and/or ovarian cancer due to family history [8, 14].
MMR	Testing for Lynch syndrome (previously known as HNPCC) includes testing of one or all of the most common mismatch repair genes (*MMR*)—*MCH1*, *MSH2*, *MSH6,* and *PMS2*. Providers use results to guide cancer prevention efforts.	(i) **EGAPP** recommends genetic testing for Lynch syndrome in individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives. They found insufficient evidence to recommend a specific testing strategy [11]. (ii) **NCCN** recommends testing for Lynch syndrome for individuals who meet certain criteria. The testing strategy will depend on whether there is a known *MMR* mutation in the family [7].
Guiding cancer treatment decisions in those already diagnosed with cancer		
BRCA	Test designed to detect specific *BRCA* mutations associated with increased risk of aggressive, recurrent cancers. Providers use results to guide treatment decisions for people with breast, ovarian, and related cancers.	(i) **NCCN** recommends *BRCA* testing when the patient meets certain personal and family breast and/or ovarian cancer history criteria [8].
Tumor gene expression profiles	Three tests, Oncotype DX, MammaPrint, and H/I ratio, are currently being marketed to help women with breast cancer and their providers make treatment decisions and estimate risk of cancer recurrence.	(i) **EGAPP** found insufficient evidence to advise for or against the use of tumor gene expression profiles in women with breast cancer [12].
CYP2D6	Test designed to help determine whether tamoxifen is likely to be a useful therapy in those with estrogen receptor-positive breast cancer.	(i) No recommendations from **EGAPP**, **NCCN**, or **USPSTF**.
MMR	Testing for Lynch Syndrome (previously known as HNPCC) includes testing of one or all of the most common mismatch repair genes (*MMR*)—*MCH1*, *MSH2*, *MSH6* and *PMS2*. Providers use the results to guide cancer management efforts.	(i) **EGAPP** recommends genetic testing for Lynch syndrome in individuals with newly diagnosed colorectal cancer. They found insufficient evidence to recommend a specific testing strategy [11]. (ii) **NCCN** recommends testing for Lynch syndrome for individuals who meet certain criteria[h].
UGT1A1	Test designed to help identify colorectal cancer patients who are at increased risk for an adverse reaction to irinotecan therapy and allow for changes in management (e.g., drug choice, dosage).	(i) **EGAPP** found insufficient evidence to recommend use of *UGT1A1* genotyping in patients with metastatic colorectal cancer treated with irinotecan [10].
KRAS	Testing for *KRAS* gene mutations may help identify colorectal cancer patients who may not respond well to *EGFR*-inhibiting drugs such as panitumumab (Vectibix) and cetuximab (Erbitux).	(i) **NCCN** recommends testing for *KRAS* tumor gene status in patients with metastatic colorectal cancer before initiating treatment with panitumumab or cetuximab [24].

from leaders from each practice group surveyed and a postage-paid screening postcard. The postcard asked if the clinician recommended screening or treated breast, ovarian, or colorectal cancer; we removed respondents who returned the postcard as ineligible from the mailing survey. The survey was sent in the second mailing via priority mail with a $10 cash incentive, postage-paid return envelope, cover letter including an electronic link of the survey (so clinicians could respond either electronically or in written form), and the endorsement letter. We did not send this second mailing to respondents who had already responded online; we sent those respondents a check for $10 separately.

In the third mailing, we sent a postcard to nonresponders with a link to the web-based survey. We made follow-up phone calls to nonresponders from both the first and the second round of survey mailings. In the survey, we asked questions about provider demographics, length of time in practice, practice setting, the provider's level of confidence in their knowledge of medical genetics, referral to genetic specialists, and use of family history to assess risk for breast, ovarian, and colorectal cancer. Portland State University Human Subjects Research Review Committee approved the survey, the informed consent process and the data collection protocol.

2.3. Survey Measures. We determined whether to ask a clinician about a particular test by the clinician's answers to four questions. (1) Providers who answered "yes" to the question, "In your practice, do you recommend breast and/or ovarian cancer SCREENING to patients without cancer?" were asked about OncoVue and *BRCA* testing. (2) Providers who answered "yes" to the question, "In your practice, do you recommend colorectal cancer SCREENING to patients without cancer?" were asked about fecal DNA and Lynch Syndrome genetic testing. (3) Providers who answered "yes" to "Do you TREAT patients for breast and/or ovarian cancer?" were asked about *BRCA*, breast cancer tumor gene expression profile, and *CYP2D6* testing. (4) Providers who answered "yes" to "Do you TREAT patients for colorectal cancer?" were asked about *MMR*, *UGT1A1*, and *KRAS* testing. Though we asked respondents whether they treat patients for cancer, these questions did not specifically define the nature of the treatment rendered. Therefore, these questions could have been interpreted to include ancillary care for pain, management of sequelae of chemotherapy or surgery, or other types of care.

When examining whether a clinician ordered a specific test, we defined "ordering" a test as actually placing an order to have the test performed. We included the term "recommending", allowing for the circumstances where (1) the provider who discusses the test with the patient is different from the provider that actually orders the test, or (2) the test is not conducted, but the provider recommended the test be done. Among providers who reported they recommended screening for breast, ovarian, or colorectal cancer, but did not order or recommend the corresponding tests, we examined their rationale for not ordering or recommending OncoVue and fecal DNA. For those who reported treating breast, ovarian, or colorectal cancer, but did not order the corresponding tests, we examined their rationale for not ordering or recommending breast cancer tumor gene expression profiles, *CYP2D6*, *UGT1A1*, and *KRAS*. Brief explanations were provided for some tests in the survey, for example, "Have you ever ordered or recommended an OncoVue test (e.g., a multigene screening panel for patients without breast cancer) to determine a patient's breast cancer risk?"

We also asked about each provider's rationale for or against ordering or recommending each of the tests. On questions regarding the rationale for ordering or recommending *BRCA* or *MMR* testing, we classified "always" "usually," or "sometimes" responses as "yes," and "never" responses as "no." We classified respondents as referring to a genetic specialist for *BRCA* or *MMR* testing if they responded that they "always" or "usually" referred to a genetic specialist. We did not ask reasons for *not* ordering or recommending *BRCA* and *MMR* testing on the survey.

2.4. Potential Covariates. We asked about potential covariates which may affect associations between genetic testing and provider group. Demographic covariates include variables such as health care providers' age, sex, years since formal training, and whether they recommend screening or treat for breast, ovarian, and colorectal cancer. Practice covariates include variables such as number of patients seen per week, practice environment, and geographic location of health care clinic.

2.5. Data Analysis. We compared respondent self-reported practice specialty and credentials to their assigned provider group (primary care providers, naturopaths, OB-GYNs, and specialists), which was based on their specialty, designated by the Oregon licensing boards. We moved surveys of three respondents from a temporary "other" category into the provider group that better reflected their practice specialty and credentials. We excluded thirty-three surveys from further analysis because the respondents indicated that they practiced in one of the provider groups that typically do not screen or treat for breast, ovarian, or colorectal cancer (e.g., emergency medicine or anesthesiology).

We classified respondents as ordering or recommending *BRCA* and *MMR* tests if they reported ordering or recommending the test at least once in the 12 months prior to completing the survey. We classified respondents who had *ever* ordered or recommended OncoVue, fecal DNA, breast cancer tumor gene expression profile, *CYP2D6*, *UGT1A1*, and *KRAS* tests as ordering or recommending these tests. We used Pearson χ^2 tests and logistic regression to assess the association between provider group and ordering or recommending cancer genetic tests, in addition to reasons why they chose to order/recommend or not order/recommend these tests.

We used logistic regression to calculate adjusted odds ratios (AOR) that compared the odds of ordering or recommending genetic testing by the provider group, using primary care providers as the referent category. Covariates were included in these models if they were significantly associated with the provider group and ordering or recommending genetic tests. We kept only covariates that changed the point estimate of the AOR by at least 10% (compared with the full model) in the final models. We did not present associations between the covariates and ordering genetic testing in this paper, as we were specifically interested in the relationship between the provider group and genetic testing. All analyses were performed using Stata version 19.0 [25]. We reported sample sizes (number of survey respondents) and percentages as unweighted numbers and estimates because the sampling methodology eliminated the need for weighting.

3. Results

Of the 2,191 health care providers who received the survey, 1,242 returned the survey fully or partially completed, giving us a response rate of nearly 57%, a gratifying response for a health care provider survey with the modest incentive of $10. We defined both paper and web surveys as being fully completed if 80%–100% of applicable questions were answered and partially completed if 50%–79% of applicable questions were answered. Though partially completed surveys were used, fully completed surveys made up more than 95% of the returned surveys. After the exclusions described in the Section 2, the final sample included 1,209 respondents. Response rates were similar among all provider groups.

Table 2(a) shows selected demographic and practice characteristics of our respondents by provider group. Among those who recommended breast, ovarian, or colorectal cancer screening, specialists were much more likely to report recommending screening patients for colorectal cancer compared to breast and ovarian cancer. Similarly, specialists were more likely to report treating patients for colorectal cancer compared to breast and ovarian cancer. About one-third of naturopaths reported that they treat patients for breast, ovarian, and/or colorectal cancer, 13% of primary care providers and 16% of OB-GYNs reported that they treat patients for breast cancer, and 13% of primary care providers reported that they treat patients for colorectal cancer. Table 2(b) outlines providers confidence in their knowledge of medical genetics by provider group. OB-GYNs had the highest level of confidence in their knowledge of breast and ovarian cancer genetics and specialists had the highest level of confidence in their knowledge of colorectal cancer genetics. Table 2(c) shows the respondent referral to a genetic specialist when they suspect a *BRCA* or *MMR* mutation by provider group. OB-GYNs and specialists had higher proportions who reported referring to genetic specialists for *BRCA* or *MMR* testing compared to naturopaths and primary care providers.

Among health care providers who report they recommend screening for breast and ovarian cancer, almost 3% reported they had ordered or recommended OncoVue at least once, and among clinicians who report recommending screening for colorectal cancer, 4% had, at least once, ordered or recommended fecal DNA screening. Among health care providers who treat breast and ovarian cancer, 28% had ordered or recommended a breast cancer tumor gene expression profile test, while nearly 9% had ordered or recommended *CYP2D6* testing. Among clinicians who treat colorectal cancer, 20% and almost 4% had ordered or recommended *KRAS* and *UGT1A1* testing respectively.

Table 3 outlines clinician likelihood to report ordering or recommending *BRCA* or *MMR* tests *in the past 12 months,* by provider group. OB-GYNs were more than twice as likely to order or recommend *BRCA* testing in the 12 months prior to completing the survey for patients without breast and ovarian cancer than primary care providers. There were no statistically significant differences between provider groups in patterns of ordering or recommending *MMR* testing for any patients or *BRCA* testing for patients with cancer. The covariates that were included in the final models are described in the footnotes of Table 3.

The reason most often reported for not ordering an OncoVue, fecal DNA, breast cancer tumor gene expression profile, *CYP2D6*, *UGT1A1*, or *KRAS* test was lack of familiarity with the genetic test. About 10% of health care providers reported that cost or insurance noncoverage was a reason for not ordering or recommending OncoVue and fecal DNA testing. In addition, 17% and 20% of providers reported that practice guidelines did not include OncoVue and fecal DNA testing, respectively. Over one-third of health care providers reported not ordering or recommending *CYP2D6*, *UGT1A1*, and *KRAS* testing because these tests were not relevant to their patients (Table 4).

A majority of clinicians who reported ordering or recommending *BRCA* testing did so for the following reasons: the patient met practice guidelines (82%–86%), to guide future screening decisions (75%–80%), to guide prophylactic management decisions (76%–80%), and because their patient requested the test (79%–81%). Clinicians gave the same reasons for ordering or recommending *MMR* testing, although the frequencies for each reason were lower than for *BRCA* testing (between 40%–73%) (Table 5).

We chose not to report reasons for ordering or recommending OncoVue and fecal DNA tests (that could be used in population-based screening for specific cancers) or breast cancer tumor gene expression profiles, *CYP2D6*, *UGT1A1*, and *KRAS* tests (that could be used to guide cancer treatment decisions), because the samples were too small to be reliable.

4. Discussion

There is a paucity of peer-reviewed studies assessing the clinical knowledge and use of the eight tests we investigated. Of all of the tests, *BRCA* has been the most studied, yet it remains underutilized. Indeed, our study suggests the likely underuse of certain tests (e.g., *BRCA* and *MMR*), which are recommended for risk stratification in people at high risk for breast, ovarian, and colorectal cancers. It also highlights important barriers to appropriate testing, such as lack of confidence in genetics knowledge and lack of familiarity with recommended genetic tests (e.g., *KRAS* testing when deciding whether to treat a patient with cetuximab). Additionally, our study suggests the appropriately low use of tests where there are either guidelines recommending against use, guidelines stating that there is insufficient information to recommend for or against use, no guidelines, or conflicting guidelines (e.g., OncoVue, fecal DNA, breast cancer tumor gene expression profiles, *CYP2D6*, and *UGTA1*).

The most common reason offered by clinicians for ordering or recommending *BRCA* and *MMR* was that the patient met practice guidelines, indicating that many providers are aware of national recommendations regarding genetic testing and consider these recommendations in making decisions about testing. Still, in settings where testing would be recommended by multiple national organizations, a sizable portion of clinicians make no reference to practice guidelines as a basis for ordering or recommending *BRCA* or *MMR* testing, suggesting that substantial gaps in awareness remain.

Table 2: Summary data from the 2010 Oregon Health Care Provider Survey, by provider group.

(a) Demographic and practice characteristics[a,b].

	PCPs[c] *n* (column %)[d] (95% CI)[e]	Naturopaths *n* (column %)[d] (95% CI)[e]	OB-GYNs *n* (column %)[d] (95% CI)[e]	Specialists[f] *n* (column %)[d] (95% CI)[e]
Total	363 (30.0%) (27.5%–32.7%)	216 (17.9%) (15.8%–20.1%)	333 (27.5%) (25.1%–30.1%)	297 (24.6%) (22.2%–27.1%)
Mean age (years)	357 (48.0 yrs) (26 yrs–76 yrs)[g]	**211 (43.5 yrs) (28 yrs–70 yrs)[g]**	329 (47.8 yrs) (27 yrs–80 yrs)[g]	288 (47.6 yrs) (27 yrs–79 yrs)[g]
Number of patients seen per week				
<50	104 (28.8%) (24.4%–33.8%)	**185 (86.4%) (81.2%–90.4%)**	103 (31.0%) (26.3%–36.2%)	127 (43.3%) (37.8%–49.1%)
50–75	129 (35.7%) (31.0%–40.9%)	25 (11.7%) (8.0%–16.7%)	126 (38.0%) (32.9%–43.3%)	121 (41.3%) (35.8%–47.0%)
>75	127 (35.5%) (30.5%–40.4%)	**4 (1.9%) (0.7%–4.9%)**	103 (31.0%) (26.3%–36.2%)	**45 (15.4%) (11.7%–20.0%)**
Recommend BOC[h] screening to patients w/o cancer	**394 (97.5%) (95.2%–98.7%)**	196 (92.0%) (87.5%–95.0%)	**326 (98.5%) (96.4%–99.4%)**	**187 (63.6%) (57.9%–68.9%)**
Recommend CRC[i] screening to patients w/o cancer	355 (98.3%) (96.4%–99.3%)	204 (95.8%) (92.1%–97.8%)	316 (94.9%) (91.9%–96.8%)	275 (93.5%) (90.1%–95.8%)
Treat patients for BOC[h]	47 (13.1%) (10.0%–17.0%)	**79 (36.9%) (30.7%–43.6%)**	53 (16.1%) (12.5%–20.4%)	**172 (58.3%) (52.6%–63.8%)**
Treat patients for CRC[i]	48 (13.3%) (10.1%–17.2%)	**63 (29.4%) (23.7%–35.9%)**	0	**241 (81.1%) (76.3%–85.2%)**

[a] Category totals may be less than the total number of respondents, due to missing values.
[b] Bolded estimates indicate significant findings.
[c] PCPs: primary care providers which include family physicians, internal medicine physicians, primary care nurse practitioners, and primary care physician assistants.
[d] The column % reflects the percent responding within each practice category.
[e] CI: confidence interval.
[f] Specialists consisted of surgeons, colorectal surgeons, general surgeons, gastroenterologists, oncologists, and gynecologic oncologists.
[g] Range in years.
[h] BOC: breast and ovarian cancer.
[i] CRC: colorectal cancer.

(b) Confidence in personal knowledge of medical genetics[a,b].

	PCPs[c] *n* (column %)[d] (95% CI)[e]	Naturopaths *n* (column %)[d] (95% CI)[e]	OB-GYNs *n* (column %)[d] (95% CI)[e]	Specialists[f] *n* (column %)[d] (95% CI)[e]
Confidence in personal knowledge of BOC[g] genetics				
Not at all	111 (30.6%) (26.1%–35.5%)	92 (42.6%) (36.2%–49.3%)	**23 (6.9%) (4.6%–10.2%)**	87 (30.0%) (25.0%–35.5%)
Somewhat	188 (51.8%) (46.6%–56.9%)	90 (41.7%) (35.3%–48.4%)	132 (39.6%) (34.5%–45.0%)	115 (39.7%) (34.2%–45.4%)
Moderately/very	64 (17.6%) (14.1%–21.9%)	34 (15.7%) (11.5%–21.2%)	**178 (53.5%) (48.1%–58.8%)**	**88 (30.3%) (25.3%–36.0%)**

(b) Continued.

	PCPs[c] *n* (column %)[d] (95% CI)[e]	Naturopaths *n* (column %)[d] (95% CI)[e]	OB-GYNs *n* (column %)[d] (95% CI)[e]	Specialists[f] *n* (column %)[d] (95% CI)[e]
Confidence in personal knowledge of CRC[h] genetics				
Not at all	110 (30.5%)	**114 (52.8%)**	77 (23.2%)	**43 (11.3%)**
	(25.9–35.4)	**(46.1–59.4)**	(19.0–28.0)	**(8.1–15.5)**
Somewhat	190 (52.6%)	81 (37.5%)	176 (53.0%)	105 (36.0%)
	(47.5%–57.7%)	(31.3%–44.2%)	(47.6%–58.3%)	(30.7%–41.6%)
Moderately/very	61 (16.9%)	21 (9.7%)	79 (23.8%)	**154 (52.7%)**
	(13.4%–21.1%)	(6.4–14.5)	(19.5–28.7)	**(47.0–58.4)**

[a]Category totals may be less than the total number of respondents, due to missing values.
[b]Bolded estimates indicate significant findings.
[c]PCPs: primary care providers which include family physicians, internal medicine physicians, primary care nurse practitioners, and primary care physician assistants.
[d]The column % reflects the percent responding within each practice category.
[e]CI: confidence interval.
[f]Specialists consisted of surgeons, colorectal surgeons, general surgeons, gastroenterologists, oncologists, and gynecologic oncologists.
[g]BOC: breast and ovarian cancer.
[h]CRC: colorectal cancer.

(c) Referral of patients to a genetic specialist[a,b].

	PCPs[c] *n* (column %)[d] (95% CI)[e]	Naturopaths *n* (column %)[d] (95% CI)[e]	OB-GYNs *n* (column %)[d] (95% CI)[e]	Specialists[f] *n* (column %)[d] (95% CI)[e]
Refer[g] patients w/o cancer to a genetic specialist for *BRCA* testing	111 (67.7%)	27 (50.0%)	225 (87.5%)	82 (75.9%)
	(60.1%–74.4%)	(36.9%–63.1%)	(82.9%–91.1%)	(67.0%–83.1%)
Refer[g] patients w/cancer to a genetic specialist for *BRCA* testing	19 (55.9%)	25 (53.2%)	40 (87.0%)	121 (75.6%)
	(39.1%–71.5%)	(39.0%–66.9%)	(73.8%–94.0%)	(68.3%–81.7%)
Refer[g] patients w/o cancer to a genetic specialist for *MMR* testing	30 (56.6%)	NA[h]	**105 (91.3%)**	122 (77.2%)
	(43.0%–69.2%)		**(84.5%–95.3%)**	(70.0%–83.1%)
Refer[g] patients w/cancer to a genetic specialist for *MMR* testing	NA[h]	NA[h]	131 (81.9%)	138 (78.0%)
			(75.1%–87.1%)	(71.2%–83.5%)

[a]Category totals may be less than the total number of respondents, due to missing values.
[b]Bolded estimates indicate significant findings.
[c]PCPs: primary care providers which include family physicians, internal medicine physicians, primary care nurse practitioners, and primary care physician assistants.
[d]The column % reflects the percent responding within each practice category.
[e]CI: confidence interval.
[f]Specialists consisted of surgeons, colorectal surgeons, general surgeons, gastroenterologists, oncologists, and gynecologic oncologists.
[g]Among providers who suspect a mutation, those who always or usually refer to a genetic specialist.
[h]Unable to report estimates due to small cell size.

It is also worth noting that many providers reported ordering or recommending *BRCA* and *MMR* testing in response to requests from patients. A 2003 study assessing the impact of a pilot direct-to-consumer marketing campaign for *BRCA* testing in Atlanta, Denver, Raleigh-Durham, and Seattle found that providers perceived an increase in patient awareness of testing, noted an increase in patient requests for testing, and ordered more *BRCA* tests, but there was no change in rate of referral to genetic specialists [26, 27]. Such referrals allow patients considered to be at high risk to receive guidance from a health professional well grounded in cancer genetics about what tests would be most appropriate, as well as pre- and post-test counseling [8, 14, 28]. Providers who do not specialize in genetics would seem to be important sources of such referrals. However, we found that one-third to one-half of primary care and naturopathic providers in our sample did not make such referrals, even when they suspected patients were at an increased risk for serious hereditary cancer syndromes.

Our finding that providers are using several genetic tests for which there are no practice guidelines highlights the need for further evaluation to determine the clinical usefulness and appropriate role of these genetic tests, including several addressed in our survey. There is some evidence that gene expression profiling tests (e.g., Onco*type* DX, MammaPrint, and H/I ratio) may help estimate risk of recurrence and guide

Table 3: Likelihood that clinicians reported ordering or recommending specific cancer genomic test *in the past 12 months*, by provider group.

	Total clinicians	PCPs[b] *n* (column %)[c] adjusted OR[d] (95% CI)[e]	Naturopaths *n* (column %)[c] adjusted OR[d] (95% CI)[e]	OB-GYNs *n* (column %)[c] adjusted OR[d] (95% CI)[e]	Specialists[f] *n* (column %)[c] adjusted OR[d] (95% CI)[e]
BRCA for patients without BC[g] or OC[h,i,j]	176 (62.6%)	51 (53.7%) 1.0 (referent)	14 (36.8%) 0.8 (0.3–1.9)	**75 (77.3%)** **2.1 (1.1–4.2)**	36 (70.6%) 2.1 (1.0–4.7)[k]
BRCA for patients with BC[g] or OC[h,i,l]	91 (63.6%)	14 (66.7%) 1.0 (referent)	14 (46.7%) 0.5 (0.1–1.7)	11 (64.7%) 0.5 (0.1–2.1)	52 (69.3%) 0.7 (0.2–2.1)
Lynch syndrome testing[m] for patients without cancer[n,o]	68 (49.6%)	9 (25.0%) 1.0 (referent)	4 (50.0%) 3.9 (0.8–20.6)	10 (50.0%) 2.6 (0.8–8.8)	45 (61.6%) 2.2 (0.7–7.3)
Lynch syndrome testing[m] for patients with cancer[n,p]	56 (61.5%)	5 (45.5%) 1.0 (referent)	NA[q]	NA[q]	50 (65.8%) 1.5 (0.4–5.5)

[a] Bolded estimates indicate significant findings.
[b] PCPs: primary care providers include family physicians, internal medicine physicians, primary care nurse practitioners, and primary care physician assistants.
[c] The column % reflects the percent responding within each practice category.
[d] OR: odds ratio.
[e] CI: confidence interval.
[f] Specialists consisted of surgeons, colorectal surgeons, general surgeons, gastroenterologists, oncologists, and gynecologic oncologists.
[g] BC: breast cancer.
[h] OC: ovarian cancer.
[i] Adjusted for number of patients seen per week and confidence in breast and ovarian cancer genetics.
[j] Among clinicians who recommend breast and ovarian screening.
[k] $P > 0.05$.
[l] Among clinicians who treat breast and/or ovarian cancer.
[m] Specifically testing for mismatch repair (*MMR*) genes, which may include testing in *MCH1*, *MSH2*, *MSH6,* and *PMS2* genes.
[n] Adjusted for confidence in knowledge of colorectal cancer genetics.
[o] Among clinicians who recommend colorectal cancer screening.
[p] Among clinicians who treat colorectal cancer.
[q] Unable to report estimates due to small cell size.

treatment decisions [12, 15, 28–30]. Testing for *CYP2D6* and *UGT1A1* genotypes are intended to identify individuals with altered functionality in genes that effect drug metabolism. Some authors have concluded that these tests may be useful to health care providers in deciding which treatments to recommend [13, 15]. However, evidence for the clinical utility of *CYP2D6* and *UGT1A1* testing is not conclusive and evidence-based national guidelines have not endorsed these tests [7, 10, 12, 28].

If a test proves to be cost effective and to lead to improved clinical outcomes, it must then be integrated into clinical practice if its potential to reduce cancer morbidity and mortality is to be realized. As we have seen in the case of *BRCA* testing, the best known of the eight tests in our study and included in national guidelines for a number of years, such an inclusion is an important but not sufficient part of this process. Other strategies include endorsement by medical societies, creation of decision support tools, and incorporation into current and continuing medical education [19, 21, 23, 31–33].

The lack of confidence by health care providers in their basic knowledge of cancer genetics is noteworthy and is consistent with other studies [17, 18, 21–23, 26]. Because of this, there is a higher chance that tests will be ordered incorrectly or inappropriately and may be misinterpreted by a nongenetic specialist, which may significantly hamper proper risk management [34]. This suggests a need for continued training to give clinicians the necessary background to know when they should order a given genetic test, how to correctly interpret the results, and in what situations patients should be referred to a genetic specialist. The higher level of confidence in breast and ovarian cancer genetics among OB-GYNs is not surprising and is consistent with research by Trivers et al., who found that being an OB-GYN was a predictor of appropriate referral to genetic specialists [35]. Others have found that specialists, such as oncologists and OB-GYNs, are often more knowledgeable about cancer genetics and cancer risk assessment than primary care providers [26, 27, 36–38]. Low levels of confidence in personal knowledge of cancer genetics, coupled with lower rates of referral to genetics specialists for high-risk patients emphasize the need for further medical genetics training, especially among primary care providers and naturopaths.

There are several limitations to this study. Firstly, given our cross-sectional study design, we could not infer causality from our data. Secondly, the survey answers were self-reported and therefore subject to recall bias. Thirdly, differences in the time interval we used for different tests in asking clinicians whether they had ordered or recommended the tests (i.e. "*ever*" or "*in the last twelve months*") limit our ability to compare the use of all eight genetic tests amongst each other. Due to small sample sizes, we were not always able to present results for the genetic tests by provider group. Finally, we did not collect information about the nature of therapy offered by respondents who reported treating breast, ovarian, and colorectal cancer. This makes reported

Table 4: Reasons why clinicians did not order or recommend various cancer genomic tests among clinicians who do not order that specific test.

	Not familiar with test *n* (%)[a] (95% CI)[b]	Clinical outcomes would not change *n* (%)[a] (95% CI)[b]	Costs too much/insurance will not cover it *n* (%)[a] (95% CI)[b]	Test not valid *n* (%)[a] (95% CI)[b]	Practice guidelines do not include this test *n* (%)[a] (95% CI)[b]	Test not relevant to patients *n* (%)[a] (95% CI)[b]
OncoVue[c,d]	787 (79.0%) (76.45%–81.4%)	24 (2.4%) (1.6%–3.6%)	106 (10.6%) (8.9%–12.7%)	11 (1.1%) (0.6%–2.0%)	173 (17.4%) (15.1%–19.9%)	75 (7.5%) (6.1%–9.3%)
Fecal DNA[e]	783 (71.8%) (69.1%–74.4%)	37 (3.4%) (2.5%–4.7%)	119 (10.9%) (9.2%–12.9%)	47 (4.3%) (3.3%– 5.7%)	216 (19.8%) (17.6%–22.3%)	57 (5.3%) (4.1%–6.7%)
Tumor gene expression profiles[f,g]	126 (50.6%) (44.4%–56.8%)	14 (5.6%) (3.3%–9.3%)	21 (8.4%) (5.6%–12.6%)	6 (2.4%) (1.1%–5.3%)	17 (6.8%) (4.3%–10.7%)	21 (8.4%) (5.5%–12.6%)
CYP2D6[g]	131 (42.1%) (36.7%–47.7%)	10 (3.2%) (1.7%–5.9%)	10 (3.2%) (1.7%–5.9%)	4 (1.3%) (0.5%–3.4%)	19 (6.1%) (3.9%–9.4%)	96 (30.9%) (26.0%–36.3)[h]
UGT1A1[i]	187 (58.4%) (52.9%–63.7%)	NA[j]	7 (2.2%) (1.0%–4.5%)	NA[j]	16 (5.0%) (3.1%–8.0%)	126 (39.4%) (34.1%–44.9%)[k]
KRAS[i]	108 (40.3%) (34.6%–46.3%)	NA[j]	4 (1.5%) (0.6%–3.9%)	NA[j]	9 (3.4%) (1.7%–6.4%)	127 (47.4%) (41.4%–53.4%)[l]

[a]The column % reflects the percent responding within each practice category.
[b]CI: confidence interval.
[c]OncoVue is a multigene screening panel for patients without breast cancer.
[d]Among clinicians who recommend breast and ovarian screening to patients without breast cancer.
[e]Among clinicians who recommend colorectal cancer screening to patients without colorectal cancer.
[f]Breast cancer tumor gene expression profiles include Oncotype DX, MammaPrint, and H/I ratio.
[g]Among clinicians who treat patients for breast cancer.
[h]Test not relevant to patients because clinician does not prescribe tamoxifen to patients.
[i]Among clinicians who treat patients for colorectal cancer.
[j]Unable to report estimates due to small cell size.
[k]Test not relevant to patients because clinician does not prescribe irinotecan to patients.
[l]Test not relevant to patients because clinician does not prescribe anti-*EGFR* therapy to patients.

Table 5: Reasons why clinicians reported ordering specific cancer genomics tests *in the past 12 months*, among clinicians who ordered the genetic tests.

	Patient met practice guidelines *n* (%)[a] (95% CI)[b]	Guide future screening decisions *n* (%)[a] (95% CI)[b]	Guide prophylactic treatment decisions *n* (%)[a] (95% CI)[b]	Patient specifically requests it *n* (%)[a] (95% CI)[b]
BRCA for patients without BC[c] or OC[d,e]	207 (85.5%) (80.5%–89.5%)	192 (79.7%) (74.1%–84.3%)	192 (79.7%) (74.1%–84.3%)	198 (81.1%) (75.7%–85.6%)
BRCA for patients with BC[c] or OC[d,f]	100 (82.0%) (74.0%–87.9%)	91 (75.2%) (66.6%–82.2%)	93 (76.2%) (67.8%–83.0%)	97 (78.9%) (70.6%–85.3%)
Lynch syndrome testing[g] for patients w/o CRC[h,i]	72 (63.7%) (54.3%–72.2%)	69 (60.5%) (51.2%–69.2%)	68 (58.6%) (49.3%–67.3%)	65 (57.0%) (47.7%–65.9%)
Lynch syndrome testing[g] for patients with CRC[h,j]	50 (72.5%) (60.5%–81.9)	46 (67.6%) (55.4%–77.9%)	27 (40.3%) (29.0%–52.7%)[k]	32 (50.0%) (37.7%–62.3%)

[a]The column % reflects the percent responding within each practice category.
[b]CI: confidence interval.
[c]BC: breast cancer.
[d]OC: ovarian cancer.
[e]Among clinicians who recommend breast and ovarian screening to patients without breast cancer.
[f]Among clinicians who treat breast and ovarian cancer.
[g]Specifically testing for mismatch repair (*MMR*) genes, which may include testing in *MCH1*, *MSH2*, *MSH6,* and *PMS2* genes.
[h]CRC: colorectal cancer.
[i]Among clinicians who recommend colorectal cancer screening to patients without colorectal cancer.
[j]Among clinicians who treat colorectal cancer.
[k]For Lynch syndrome testing for patients with cancer, the phrasing was "guide chemotherapeutic treatment decisions."

differences in the frequency of treating such patients difficult to interpret. Higher rates of cancer treatment reported by naturopaths compared with primary care providers or OB-GYNs may involve the perception that naturopathic efforts to improve the patient's overall health are a component of cancer treatment, a view that may not have been shared by most allopathic clinicians providing services other than surgery or chemotherapy.

5. Conclusion

Reducing morbidity and mortality due to breast, ovarian, and colorectal cancers is a laudable goal. Consistent use of evidence-based genetic tests could contribute to that objective, while underutilization of these tests limits their potential contribution. Perceived low levels of knowledge about relevant genetics appear to be an obstacle both to the use of these tests and to the timely referral to genetic specialists. Clinicians working in settings with higher volumes of cancer patients note higher levels of confidence in relevant knowledge of medical genetics, but even then, almost half report low confidence in their knowledge base. Education through multiple modalities is a reasonable strategy to address these perceived knowledge deficits. At this time, the appropriate role of several genetic tests is undetermined, but for some genetic tests (e.g., *BRCA* and *MMR*) the cost effectiveness, efficacy in guiding preventive care and treatment, and beneficial health outcomes have been demonstrated. Continued evaluation of emerging technologies and subsequent dissemination of information about the clinical utility, interpretation, and indications for the use of such tests are necessary to ensure their integration into appropriate patient care.

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Endnotes

1. Generally, a "genetic" test assesses for the presence or effect of a single gene, while a "genomic" test assesses the presence or activity of multiple genes. In this paper, we will use the term "genetic tests" and "genetic testing" to describe both genetic and genomic tests.

2. The American College of Surgeons' Commission on Cancer has recently published new cancer program standards. These standards require that cancer risk assessment, genetic counseling, and testing services be provided to patients by a qualified genetics professional. The standards also outline the criteria for pre- and post-genetic counseling and define the training and experience of qualified genetics professionals, whom we refer to as "genetic specialists". The Cancer Program Standards 2012: Ensuring Patient-Centered Care is available at http://www.facs.org/cancer/coc/cocprogramstandards2012.pdf. See especially Standard 2.3, Risk Assessment and Genetic Counseling on pg 68.

3. Naturopathic physicians use a whole-body and minimally invasive approach with the goal of restoring the health of their patients; their model of care avoids drugs and surgery and emphasizes the use of natural agents and physical means (http://www.merriam-webster.com/medical/naturopathy).

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Research Article

Barriers and Facilitators for Utilization of Genetic Counseling and Risk Assessment Services in Young Female Breast Cancer Survivors

Beth Anderson, Jennifer McLosky, Elizabeth Wasilevich, Sarah Lyon-Callo, Debra Duquette, and Glenn Copeland

Michigan Department of Community Health, 201 Townsend, P.O. Box 30195, Lansing, MI 48909, USA

Correspondence should be addressed to Beth Anderson, andersonb@michigan.gov

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Introduction. Women diagnosed with breast cancer at a young age are more likely to carry a cancer predisposing genetic mutation. Per the current NCCN recommendations, women diagnosed under age 50 should be referred to cancer genetic counseling for further risk evaluation. This study seeks to assess patient-reported barriers and facilitators to receiving genetic counseling and risk assessment among a community-based population of young breast cancer survivors (YBCS). *Methods*. Through the Michigan Cancer Surveillance Program, a state-based cancer registry, 488 women diagnosed with breast cancer before age 50 in 2006-2007 were identified. They received a mail survey regarding family history and facilitators and barriers to receiving genetic counseling and risk assessment. *Results*. Responses were received from 289 women (59.2%). One hundred twenty-two (42.2%) reported having received cancer genetic counseling. The most frequent reason identified for receiving services was to benefit their family's future. The top reasons for not attending were "no one recommended it" and "medical insurance coverage issues." *Discussion*. This study is the first published report using a state cancer registry to determine facilitators and barriers to receiving genetic counseling and risk assessment among YBCS. These findings demonstrate the need for additional awareness and education about appropriate indications for genetic services.

1. Introduction

Breast cancer diagnosed at a young age is an indication of a higher likelihood for an inherited cancer syndrome, such as hereditary breast and/or ovarian cancer syndrome (HBOC) or rarer genetic conditions such as Cowden syndrome and Li-Fraumeni syndrome [1–3]. According to the 2011 National Comprehensive Cancer Network (NCCN) Guidelines entitled "Genetic/Familial High-Risk Assessment: Breast and Ovarian," women diagnosed with breast cancer prior to age 50 should be referred for further risk assessment, genetic counseling, and possible genetic testing [3]. Individuals diagnosed with breast cancer prior to age 50 are commonly referred to as young breast cancer survivors (YBCS) [4]. YBCS remain an understudied survivor population who have unique needs and challenges compared to the traditional cancer survivors because of young ages at diagnosis and associated family and societal roles [5, 6]. Even less is known about factors motivating this young population to attend a familial/high risk genetic counseling clinic.

According to the recent cancer genetic counseling recommendations published by the National Society of Genetic Counselors (NSGC), "genetic counseling and risk assessment is the process of identifying and counseling individuals at increased risk of developing cancer and distinguishing between those at high risk (highly penetrant hereditary cancer syndrome), those at modestly increased risk (multifactorial etiology or low penetrance allele), and those at average risk" [7]. Genetic counseling and risk assessment are often obtained through referral to a qualified cancer genetic professional [8]. Recent studies have found that referring providers are not able to consistently recognize appropriate referral indications for hereditary breast and ovarian cancer risk assessment and genetic counseling [2, 9–11].

As recommended by the NSGC and others, the essential components of the hereditary cancer risk assessment and genetic counseling visit include: (1) patient intake, including personal medical and 3-4 generation family history; (2) cancer genetic risk assessment using the personal history, family history, and physical examination to determine average, moderate, or increased cancer risk; (3) the offer of genetic testing when appropriate conditions apply; (4) an informed consent process is necessary and, in Michigan, legally required; and (5) disclosure of test results, including personalized interpretation of results, cancer risk reassessment, and identification of at-risk family members regardless of whether the test is positive, negative, or inconclusive [3, 7, 9, 12]. Qualified cancer genetics professionals guide patients through these essential components as well as encourage women at high risk to adopt appropriate screening and preventive strategies, since individuals with HBOC may benefit from earlier detection or more intense cancer screening or intervention [3, 7, 12, 13].

Six key prior studies have been published on motivators, facilitators, and/or barriers to patients attending familial/high risk cancer clinics, genetic counseling, and risk assessment using varying populations and recruitment methods [13–19]. Four of these studies took place outside the United States. Brain et al. conducted the largest study to date, using questionnaires from 833 Welsh women, all with a family history of breast cancer, to identify self-reported reasons for attending a familial breast cancer clinic; among the reasons identified for attending, personal risk was ranked highest, followed by risk to family members, to gain reassurance, and interest in genetic testing. Chin et al. (2005) looked specifically at female breast cancer survivors and evaluated responses to a hypothetical question about willingness to attend breast cancer genetic risk assessment clinic. Among 164 Singaporean female breast cancer survivors of all ages from a clinical population, the top facilitator identified was "the information may help my family understand their cancer risk"; the top barriers identified were the perception of no benefit, since this population was already affected, and the cost of such services [13]. A national multicenter study in England conducted by Fraser et al. surveyed 162 men and women, both affected and unaffected with cancer, who were referred to one of five regional cancer genetics centers. They found clear differences in personal motivation for referral follow-through between those with and those without cancer and found the main motivation for attending clinic in those with a personal history of cancer was altruistic concern for their family members and children [17]. A unique study by Wakefield et al. recruited 39 adult family members of all ages with a family history of hereditary breast and ovarian cancer syndrome (HBOC) due to a genetic mutation in *BRCA* genes [14]. In this Australian study, the top facilitators for cancer genetic referrals were the desire for *BRCA* testing and having a strong family history of breast and/or ovarian cancer. The top barriers were lack of awareness of the *BRCA* mutation in their family and appropriateness of referral [14].

Two studies were conducted within the United States. Morgan et al. recruited 69 adult women of all ages at risk for HBOC who had received genetic counseling and risk assessment in Maine. In this US study, the top facilitators to receiving genetic counseling and risk assessment were having a family history of breast and/or ovarian cancer and having a personal history of cancer [15]. Barriers to services were not evaluated in this study. Pal et al. (2011) worked with the Florida state cancer registry to recruit 82 young black breast cancer survivors for genetic counseling and *BRCA 1* and *2* genetic testing to demonstrate that young black women are interested in participating in genetic studies [18].

None of the studies above were carried out strictly on young women with breast cancer (under age 50 at diagnosis). Despite study efforts to obtain surveys prior to attendance at familial/high risk cancer clinics, the studies above used data from women who had already been referred for genetic risk assessment except for one study that used a hypothetical referral situation. None of these studies were able to evaluate the facilitators and barriers to accessing genetic services in a general patient population with unknown genetic referral status.

To our knowledge, this study is the first to look at the facilitators and barriers to referral for and receipt of genetic counseling and risk assessment in YBCS. It is also the largest of its kind to look at issues related to YBCS utilizing a US state cancer registry. For our study, facilitators are defined as internal and external motivating factors to receiving services, and barriers are defined as internal and external inhibiting factors to receiving services. The objective of this study is to examine the number of YBCS who self-report having been referred for genetic services (genetic counseling and risk assessment) and to determine the self-reported barriers and facilitators to receiving these services, within a representative state cancer registry sample.

2. Methods

2.1. Selection Process. The sampling frame included women between the ages 18–49 who were diagnosed with invasive and noninvasive breast cancer in the years 2006 or 2007 in the state of Michigan. The eligible population was selected from the Michigan Cancer Surveillance Program (MCSP) registry, which has a mandate to collect data from local reporting facilities on cases of cancer and other specified tumorous and precancerous diseases that occur in the state. The study team worked with MCSP to exclude women who were known to be deceased from the state vital records. Of the 3,911 YBCS diagnosed in 2006 and 2007, 500 women were selected by simple random selection from the eligible population. Prior to implementation, the Michigan Department of Community Health's Institutional Review Board and the MCSP's Scientific Advisory Board reviewed and approved the study.

2.2. Consent Process. The consent process consisted of three steps based on an existing standard method used by MCSP (Figure 1). The first step was MCSP notifying the local reporting facility regarding the YBCS survey and requesting information regarding the physician on record. MCSP then contacted the physician on record regarding the YBCS survey. Both were provided with the potential study participant's

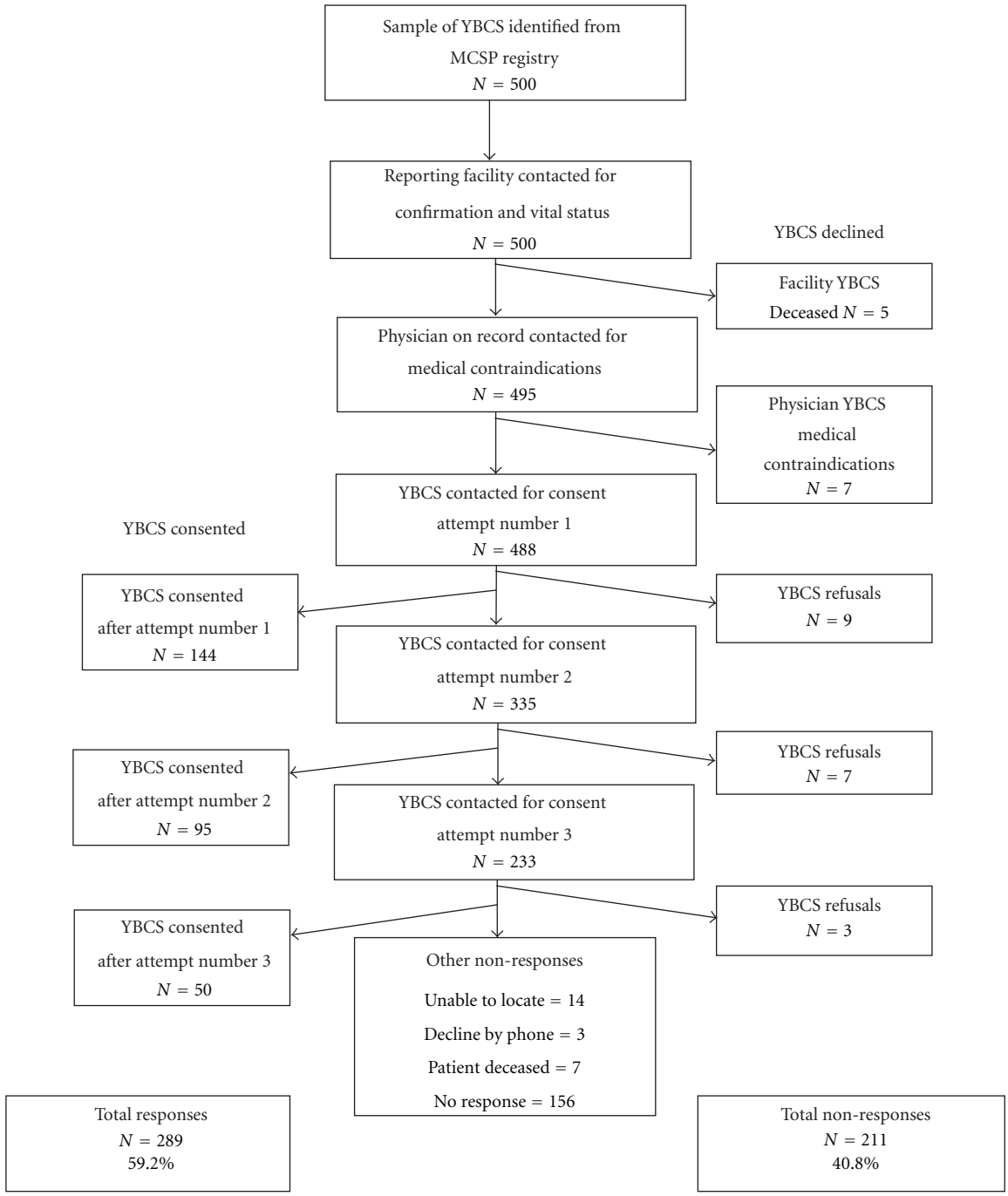

Figure 1: Flow chart of the selection and consent process.

name and the physician on record was asked whether they knew of any reason that the selected participant should not be contacted such as death, mental illness, or illness due to current cancer treatments. If the local reporting facility and diagnosing physician confirmed their case and the physician did not indicate any medical contraindications, to MCSP contacting their patient, the participant was mailed the survey making up to three attempts to obtain a response.

The survey mailings included a personalized cover letter inviting participation and a postage-paid reply envelope. Due to budget constraints, the survey was in English only and was self-administered. The respondent was asked to sign an informed consent attached to the survey. Participants who returned a signed consent form and survey were mailed a $10 gift card. At all times, the participant's identifiable information was unavailable to the study team; only MCSP staff could identify the participants.

2.3. Survey Development. A review of available surveys was performed, and six surveys were obtained from several

principle investigators of prior studies [20–25]. It was determined that no single prior tool was appropriate for our study in its entirety given the state-based, young survivor population and need for a self-administered mail survey; thus, a new tool was developed. Validated demographic questions from the National Behavioral Risk Factor Survey were used. The remaining questions were both adapted from the cited tools and created to fit our study methodology as a paper-based mail survey for young women that have survived a breast cancer diagnosis and to fulfill our study objectives.

The survey contained 31 questions, including fixed-choice and write-in response items. Within the survey "cancer genetic services" were defined for the patient (Box 1); this description was generated from several brochures and definitions and was meant to be a general description so that a patient might recognize whether they have had genetic counseling and risk assessment [26–29]. Respondents were asked if anyone had ever suggested that they go to cancer genetics services and if they ever received cancer genetic services. Based on this self-report, women who stated they had received services were asked about facilitators for receiving services ("please tell us why you decided to go for cancer genetics services?" and "please tell us what factors made it easier for you to go for cancer genetics services?"). The first question included fixed-choice responses related to psychological responses (to benefit my family, to reduce my cancer risk, etc.) and the second question addressed physical facilitators making it easier to go (e.g., time off work, transportation, and medical coverage). Women who stated they had not received services were asked about barriers to receipt ("Please tell us why you have not had cancer genetics services"). The main questions used to assess barriers and facilitators to receiving services were written by the study team; these questions and the fixed-choice response items for these questions are shown in the Appendix. Items included in the fixed-choice responses for both the barriers and facilitators were a collection of choices from the literature, expert opinion from the project steering committee members, and cancer survivors' input on the survey pilot (see below).

2.4. Survey Pilot. Survey drafts were extensively reviewed by the experts at MDCH Cancer Prevention and Control Section, the Centers for Disease Control Prevention Office of Public Health Genomics, MDCH Health Disparities, MDCH Disabilities, and the MDCH Project Steering Committee comprised of clinical geneticists, oncologists, genetic counselors, a health plan specialist, patient advocates, an advanced practice nurse, and epidemiologists.

The survey was piloted with four YBCS and one individual with a *BRCA* mutation. Pilot participants were asked to complete the survey in one sitting and track the length of time it took to complete. Following completion, they were asked to comment on any sections, questions, or answer choices that were unclear/unnecessary, uncomfortable, require different phrasing, require an alternative answer choice, or should be changed in some way. Several changes were made to question wording and survey format based on pilot responses, but overall survey length and content were retained.

2.5. Analysis. Response frequencies were assessed for differences between groups defined by demographic characteristics, socioeconomic characteristics, and family history of cancer. Two-sided Pearson chi-square tests were used to determine significant differences between subpopulations; P-values of <.05 were considered statistically significant. Multivariable logistic regression analysis was conducted to assess associations between demographic predictors and receipt of genetic counseling and risk assessment by using adjusted odds ratios with 95% confidence intervals. Likelihood chi-square tests were used to detect bivariate associations; P-values of <.05 were considered statistically significant. Demographic predictors in the analysis were employment, education, insurance, race, family history, and age at breast cancer diagnosis; all variables were categorical. Forward stepwise selection was used to populate the model. All analyses were conducted using PASW Statistics version 18.0 (IBM Corporation, NY, 2009).

3. Results

3.1. Sample Population. Five hundred women were sampled from the eligible population of 3,911 by MCSP. There were no statistically significant differences in age and racial characteristics between the sample and eligible population (Table 1). Based on local cancer registries and provider responses, 12 women were determined to be ineligible for the study, including five who were deceased and seven who had medical contraindications preventing contact (Figure 1).

Surveys and consent documents were sent to the remaining 488 women in the sample. In total, 199 women who were sent surveys did not respond; 22 declined by phone or mail, 14 were unable to be located by mail, 7 were deceased, and 156 had no response, Figure 1. Surveys and signed consents were received from 289 women, for a response rate of 59.2%. The response rate from the black population (35.8%) was much lower than the response rate from the white population (64.0%) (data not shown).

Age, race, and cancer stage reported in the MCSP database was used to compare the respondent and nonrespondent populations. The racial distribution between these two populations was significantly different ($P < .001$) with blacks having a lower response rate than whites.

3.2. Demographics among Respondents. Respondents were primarily white (86.2%), employed for wages (56.1%), had private insurance (75.4%), had a college degree or higher (50.2%), and had a family history of breast and/or ovarian cancer in a first or second degree relative (53.3%) (Table 2). Mean age at breast cancer diagnosis was 43 years with a range of 26–49 years. Almost three-quarters of the YBCS had been diagnosed with invasive breast cancer in 2006 or 2007 (70.6%) (Table 1). Forty-three YBCS had more than one cancer diagnosis and 34 of them had a second breast cancer diagnosis (data not shown).

Cancer genetics services help patients to know if the cancer in their family might have been inherited (hereditary cancer). The visit often includes the following.
(i) Collection of medical and family history information.
(ii) The history is used to find out a patient's risk for cancer and the chance that the cancer in the family has an inherited cause (passed down in the family).
(iii) The patient is given facts about inherited cancers and other causes of cancer.
(iv) The patient is told about genetic testing, pros and cons of testing, possible genetic test results, and what each test result means for their future and for their family members.
(v) The patient is given information about ways they can screen for and reduce their risk of cancer.
(vi) Medical insurance coverage of genetic testing is talked about before a test is ordered.
(vii) The patient is given a choice to have or not have genetic testing. If they choose testing, they are helped with getting the test and understanding the results.

Box 1: The definition of "cancer genetics services" provided to the YBCS in the survey instrument.

Table 1: Demographics of the young breast cancer survivors from the registry and the random sample that was selected for the study.

	YBCS population $N = 3{,}911$	Sample population $N = 500$	Respondent population $N = 289$	Nonrespondent population $N = 211$
Age	44.62 (20–49)	43.02 (20–49)	43.04 (26–49)	43.01 (20–49)
Race				
White	3,218 (82.3%)	399 (79.8%)	249 (86.2%)	150 (71.1%)
Black	531 (13.6%)	69 (13.8%)	24 (8.3%)	45 (21.3%)
Other	103 (2.6%)	32 (6.4%)	16 (5.5%)	16 (7.6%)
Cancer stage				
Invasive	2,915 (74.5%)	358 (71.6%)	204 (70.6%)	154 (73.0%)
Noninvasive	996 (25.5%)	142 (28.4%)	85 (29.4%)	57 (27.0%)

One hundred twenty-two respondents (42.2%) reported receiving genetic counseling and risk assessment. Compared to those who did not receive genetic counseling and risk assessment ($n = 158$), the women who received services were of a younger age ($P = .002$), higher education ($P = .033$), and were more likely to report having a family history of breast and/or ovarian cancer ($P = .001$) (Table 2).

Over half of the women (51.6%) who received genetic counseling and risk assessment perceived that the risk for breast cancer in their family was higher than other families, compared to 35.4% of women who did not receive genetic services (data not shown). Trouble keeping follow-up cancer treatment appointments was more frequent among women who did not receive genetic counseling and risk assessment (14.6%) than women who did receive genetic counseling and risk assessment (8.2%) (data not shown).

3.3. Predictors and Facilitators to Receiving Genetic Counseling and Risk Assessment. Among the 122 women who received genetic counseling and risk assessment, the most frequently cited reasons for going to genetic counseling and risk assessment were "benefit my family's future" (86.1%), followed by "wanted to know my future risk of cancer" (50.8%), "my doctor recommended that I go" (41.0%), and "may alter my cancer treatment" (39.3%) (Table 3).

Of the women who received services and mentioned that genetic counseling and risk assessment would benefit their family's future, 54.1% had a reported family history of breast and/or ovarian cancer.

Among women who received genetic counseling and risk assessment, the top three reported factors that made it easier to go for genetic counseling and risk assessment were "medical insurance covered the visit" (68.0%), "the clinic was close to home" (40.2%), and "have available transportation" (40.2%) (Table 3). Due to small sample sizes, it was not possible to explore differences in demographics.

Importantly, of the 122 women who received the genetic counseling and risk assessment, 121 were told or recommended by a health care professional or family member to go and one was never told about these services. The majority were told by an oncologist (48.4%) or surgeon (19.7%). A small number of women were told by their OB/GYN (4.9%), genetic counselor (4.9%), or family member (4.9%).

Of the 289 respondents, 50 were excluded from the multivariate logistic regression analysis due to missing data, leaving 239 cases in the analysis. In the final logistic regression model, family history of breast and/or ovarian cancer (odds ratio = 2.308, P-value = .002) and young age at the time of breast cancer diagnosis (odds ratio = 5.008, P-value = .006) were associated with receiving genetic services (Table 4). No further variables were added to the model because the parameter estimates changed by less than .001. The goodness of fit for this final model had a chi-square score of .001 with a P-value equal to .975, and the model accounted for 55.6% of the variation in the outcome.

3.4. Barriers to Receiving Genetic Counseling and Risk Assessment. Among the 158 women who did not receive genetic

Table 2: Demographics of YBCS respondents.

	Study population $N = 289$ (100%)	Received genetic counseling $N = 122$ (42.2%)	Did not receive genetic counseling $N = 158$ (54.7%)	
Age at diagnosis (yrs)				
20–34	22 (7.6%)	17 (13.9%)	5 (3.2%)	$P = .002$
35–49	266 (92.0%)	105 (86.1%)	152 (96.2%)	
Race				
White	249 (86.2%)	110 (90.2%)	132 (83.5%)	$P = .205$
Black	24 (8.3%)	5 (4.1%)	17 (10.8%)	$P = .075$
Other	16 (5.5%)	7 (5.7%)	9 (5.7%)	$P = .995$
Employment*				
Employed for wages	162 (56.1%)	70 (57.4%)	88 (55.7%)	$P = .845$
Self-employed	14 (4.8%)	6 (4.9%)	7 (4.4%)	$P = .893$
Out of work	15 (5.2%)	5 (4.1%)	10 (6.3%)	$P = .503$
Unable to work	32 (11.1%)	11 (9.0%)	18 (11.4%)	$P = .383$
Other	37 (12.8%)	21 (17.2%)	16 (10.1%)	$P = .566$
Insurance (time of *dx*)**				
Private	218 (75.4%)	102 (83.6%)	112 (70.9%)	$P = .175$
Government	15 (5.2%)	5 (4.1%)	9 (5.7%)	$P = .660$
None	11 (3.8%)	2 (1.6%)	7 (4.4%)	$P = .173$
Multiple	14 (4.8%)	3 (2.5%)	10 (6.3%)	$P = .112$
Education				
High school diploma or less	57 (19.7%)	13 (10.7%)	40 (25.3%)	$P = .003$
Some college	83 (28.7%)	39 (32.0%)	41 (25.9%)	$P = .222$
College degree	102 (35.3%)	47 (38.5%)	53 (33.5%)	$P = .576$
Graduate degree	43 (14.9%)	21 (17.2%)	22 (13.9%)	$P = .351$
Family history of cancer***				
Yes	154 (53.3%)	79 (64.8%)	71 (44.9%)	$P = .001$
No	135 (46.7%)	43 (35.2%)	87 (55.1%)	

*Data missing for 29 respondents.
**Data missing for 31 respondents.
***Family history of breast or ovarian cancer in a first or second degree relative.

counseling and risk assessment, the top barriers reported were "no one ever recommended it" (58.2%), "medical insurance coverage issues" (23.4%), "did not know they existed" (10.8%), and "worried a genetic test could be used against me" (9.5%) (Table 5). Among the 37 women who reported that medical insurance coverage issues were at least one reason they did not receive genetic counseling and risk assessment, 62.2% had private insurance, 13.5% were self-insured, 10.8% had no insurance, 5.4% had Medicare, and 2.7% had Medicaid coverage (data not shown). As mentioned above, when asked "Has anyone ever suggested that you should go for cancer genetics services?" 72.9% of women who did not receive genetic counseling and risk assessment reported that no one had recommended they do so. Yet only 58.2% of the women that did not receive genetic counseling and risk assessment reported it as a barrier when asked to list the reasons for not having cancer genetic counseling and risk assessment later in the survey.

4. Discussion

This project marks the largest published report using a US state cancer registry to survey YBCS (diagnosed under age 50). This study documents patient-reported referral history for genetic counseling and risk assessment and facilitators and barriers to receiving those services. The use of a state cancer registry as a sampling frame is a unique method to recruiting YBCS and surveying them on their referral history for genetic counseling and risk assessment. This method provided results representative of a cancer survivor population, and the MCSP procedures proved to be effective, with nearly 60% of those contacted responding to a mail survey. We speculate that our strong response rate might be due to this population being so personally invested in the survey topic; several comments were written on the surveys with one woman stating, "Thank you. This is a very important topic."

Table 3: Reasons for going to genetic counseling and risk assessment and factors that made it easier.

	$n = 122$ (42.2%)
Reasons for going*	
Benefit my family's future	105 (86.1%)
Wanted to know my future risk of cancer	62 (50.8%)
My doctor recommended that I go	50 (41.0%)
May alter my cancer treatment	48 (39.3%)
Going seemed very important	41 (33.6%)
Family members wanted me to go	21 (17.2%)
Already knew of a familial mutation	3 (2.5%)
Factors that made it easier to go**	
My medical insurance covered the visit	83 (68.0%)
Clinic was close to home	49 (40.2%)
Have available transportation	49 (40.2%)
Clinic hours were flexible and fit my schedule	30 (24.6%)
Have available childcare	11 (9.0%)
I was able to obtain these services by phone	2 (1.6%)

*Among the 122 respondents who answered the question "please tell us why you decided to go for cancer genetics services".
**Among the 122 respondents who answered the question "please tell us what factors made it easier for you to go for cancer genetics services?".
On average YBCS reported 2.7 reasons that they went.
On average these women reported 1.8 reasons that made it easier for them to go.

Previously published studies have used varying populations and survey methods to examine facilitators and barriers to receiving genetic counseling and risk assessment [13–17, 19]; however, our study that included 289 YBCS is the largest US study to date. Although Pal et al. (2011) used a similar sampling frame and found the same primary factor for being interested in cancer genetic counseling and testing among their 82 young black female participants (for the sake of their family members), their use of the state cancer registry in Florida was somewhat different than our use of the MCSP registry. Due to the nature of the Pal study with the involvement of DNA collection, recruitment methods were more extensive, involving eventual telephone contact to enroll patients and trained staff time [18]. For the purposes of data collection, the mail-only methods of our survey produced a higher response rate and would be easier and more economical for replication at other state cancer registries throughout the country.

4.1. Facilitators to Receiving Genetic Counseling and Risk Assessment. A common theme in Michigan and other studies was the role of the survivor's family in the decision to receive genetic counseling and risk assessment [13–18]. Michigan women reported "benefit my family's future" as their top reason for receiving genetic counseling and risk assessment. Other studies found similar motivating factors, including "helping the family understand their cancer risk" [13], "helping the family make better health decisions" [13], and "to better understand the risk of cancer in family members" [18].

"Wanting to know future risk of cancer" was the second most noted facilitator in this Michigan study, which is similar to previous studies [13, 16, 17]. Chin et al. found that the top reasons listed as motivators to attend breast cancer genetic clinics were "learning what to do to detect cancer early", "learning how to reduce cancer risk", and "understanding cancer risk" [13]. Brain et al.'s top motivator for attending a familial breast cancer clinic was "to find out about my risk" [16]. Identifying individuals at risk of developing a future cancer can have dramatic effects on early detection and cancer outcomes, which is one reason why genetic counseling and risk assessment are becoming a standard of care [9].

In previous studies, having a family history of breast and ovarian cancer was identified as a common reason for women with a personal or family history of breast cancer to go to genetic counseling and risk assessment [14, 15]. Our study was able to expand upon these findings to show that significantly more women with a family history of breast or ovarian cancer reported receiving genetic counseling and risk assessment than those that that did not have a family history. Based on our survey responses, it is unknown whether this family history was ever shared with a healthcare provider. This is an area for possible future exploration.

The role of a healthcare provider has been shown to be a strong facilitator for receiving genetic counseling and risk assessment [13, 15] and was seen in our study as the third most noted facilitator. Approximately three-quarters of the Michigan YBCS who were told to go to genetic counseling and risk assessment followed through with this recommendation. Chin et al. reported that 85% of breast cancer patients cited "if the doctor asked me to" would be an important motivator [13].

Given the influential role of healthcare providers in motivating patients to receive genetic counseling and risk assessment, there is a need for additional provider education regarding appropriate indications for cancer genetic referrals. A recent survey of primary care physicians showed that 87% were aware of *BRCA* genetic testing and 25% reported ordering a test in the last year; however, less than one-fifth correctly identified the low and high risk clinical scenarios they were given [9]. All of our study participants are appropriate for referral to genetic counseling based on age at diagnosis alone (under age 50 with breast cancer). However, over 40% report that their provider never recommended that they go. Our study clearly reinforces the need to educate providers regarding the potential benefits of genetic counseling and risk assessment for appropriate patients such as YBCS.

4.2. Barriers to Receiving Genetic Counseling and Risk Assessment. The most frequently reported barrier among the study population was that "no one had ever recommended" genetic counseling and risk assessment to the YBCS. Similarly, Fraser and colleagues reported that more than half of their patients were the first to raise the issue of their family history of cancer to their provider [17]. Lack of provider recognition of high risk family history is an important concern identified in this and other studies. Trivers et al. (2011) surveyed 3,200 US family physicians, general internists, and OB/GYNs and

Table 4: Final logistic regression model for receiving genetic counseling and risk assessment.

	Model 1				Model 2			
	B	*P*	Odds ratio	95% CI	*B*	*P*	Odds ratio	95% CI
Family history	.860	.001	2.362	1.399–3.988	.837	.002	2.308	1.353–3.938
Age 20–34					1.627	.006	5.088	1.607–16.108

Hosmer and Lemeshow chi-square test = 0.001, *P value* = .975.

Table 5: Reasons for not having genetic counseling and risk assessment*.

	$n = 158$ (54.7%)
No one ever recommended it	92 (58.2%)
Medical insurance coverage issues	37 (23.4%)
Did not know they existed	17 (10.8%)
Worried a genetic test could be used against me	15 (9.5%)
Too nervous	6 (3.8%)
A doctor told me not to go	5 (3.2%)
Lack of transportation	4 (2.5%)
Other life arise that are more important	4 (2.5%)
Too busy	3 (1.9%)
Disability makes it difficult to carry out daily activities	2 (1.3%)
Family members wouldn't want me to go	2 (1.3%)

*Among the 158 respondents who answered the question "please tell us why you have not had cancer genetics services?".
The average number of barriers reported among these women was 1.2.

found that among high risk women, only 41% of physicians self-reported recognizing high risk women and adhering to referral recommendations for genetic counseling or testing. Providers have a harder time correctly identifying high-risk women (41% of the time they assess the patient risk correctly) compared to average-risk women (71% of the time they assess the patient risk correctly) [10]. Provider understanding and awareness can be improved through promotion of current evidence-based and nationally accepted practice guidelines on hereditary breast and ovarian cancer [3].

Our study found that YBCS without a family history of breast and/or ovarian cancer were less frequently receiving a referral for genetic counseling and risk assessment, although they are appropriate for referral based solely on age at diagnosis [3, 8, 28]. Additionally, YBCS in the 35–49-year-old age group were the most likely age group to be missed. It appears that being a YBCS of a younger age and/or having a family history of breast and/or ovarian cancer is more obvious to providers and more likely to prompt identification of a need for referral. It is not known if this is related to provider and/or patient motivators; this is another area in need of future research. It is possible that providers are more aware of indications for HBOC testing and are not aware of the broader indications for appropriate referral for cancer genetic counseling.

Medical insurance coverage issues were another factor influencing referral and receipt of genetic counseling in this study, both as a facilitator to receiving services and a barrier for not attending. Although the recent passage of the Affordable Care Act provides coverage by health insurers for those with a family history of breast and/or ovarian cancer [30], another potential area of future research is to compare our findings to countries with national health insurance for cancer survivors to receive genetic counseling and risk assessment.

With the success of reducing cancer mortality, there is now an increasing number of YBCS; this population has a unique and complex set of roles (i.e., patient, mother, worker, caregiver) with personal barriers such as lack of time due to family responsibilities and appointment fatigue [8]. In our study, it appears that the population who did not make it to genetic counseling and risk assessment also had a harder time making it to their cancer-related follow-up appointments. The use of a patient navigator model in cancer genetic referral has been suggested by Rahm et al. and could help to address this barrier and increase utilization [31].

The fourth most reported barrier to genetic counseling and risk assessment was "worried a genetic test could be used against me." In 2008, the Genetic Information Non-Discrimination Act (GINA) was passed as a federal law and is currently enforced by various federal agencies [32]. GINA provides protection against discrimination in health coverage and employment on the basis of genetic information [32]. In order to address this barrier, additional patient and provider education about this federal protection would be of importance.

4.3. Limitations. Although the random sample was representative of Michigan YBCS, the response rate was significantly lower among blacks than whites (35.8% and 64.0% resp.), meaning that the generalizability of the results to other black YBCS women may be poor.

We do not have an explanation for this reduced response rate in our black population. According to Wendler et al. (2006), who carried out an extensive literature review of racial and ethnic minorities and their willingness to participate in health research, there are very small differences in the willingness of minorities to participate [33]. However, according to Simon and Petrucelli (2009), the literature suggests the presence of a number of barriers to the use of genetic services in the African American community, including lack of knowledge of genetics, adverse attitudes regarding genetics, and fears of racial discrimination [34]. MDCH will therefore be examining additional details about the non-respondents and the racial differences in the response rate in the future.

This study was meant to address all women with YBCS. However, 12 women were deceased and could not participate

in our study. It is not known if referral for cancer genetic counseling and risk assessment was ever received.

Another limitation was that the survey was only offered in English. However, in Michigan, the number of individuals who do not speak and understand English is lower than the national average (Michigan 3.2% of population versus US 8.1% of population) [35].

A batch of surveys was mailed out that was missing a page of the survey. That page included questions on employment, insurance, and race. These women were sent the missing page asking them to return it. However, 29 women did not return it; therefore, the demographic information is missing on several women.

Due to the cross-sectional nature of the survey, there may have been response bias wherein women who had been to cancer genetic services prior to taking the survey were more likely to participate. In addition, women who had a family history of cancer may have been more likely to remember having received cancer genetic services. A prospective study starting at the time of diagnosis would be the best method to examine YBCS' perception of the importance of cancer genetic services and the facilitators and barriers to receipt of such services. Also, an analysis that includes likelihood for HBOC based on pathology and extensive family history would be beneficial for future studies.

5. Conclusions

This is the first study that provides community-based information about barriers and facilitators to obtaining genetic counseling and risk assessment among YBCS. Results point to the need for promotion and education outreach to providers about the national guidelines and the importance for referral to genetic counseling and risk assessment. Provider practice could also be enhanced through policies that encourage appropriate genetic counseling and risk assessment referrals and through creation and dissemination of patient and provider cancer genetic resources and tools for risk assessment and referral. The results also indicate a need for increased service promotion to YBCS on what is available to them and how the cost of the services can be covered. Policies to improve use and access to genetic counseling and risk assessment need to be explored and initiated to help detect cancer earlier and reduce mortality.

Appendix

Survey Instrument Questions Used in This Article Related to Receiving Genetic Counseling and Risk Assessment

(i) Has anyone ever suggested that you should go for cancer genetics services?

- ☐ Yes
- ☐ No
- ☐ Don't know

(ii) Have you ever had cancer genetics services?

- ☐ Yes
- ☐ No
- ☐ Don't know

(iii) Please tell us why you have not had cancer genetics services? (Check all that apply)

- ☐ No one ever recommended it
- ☐ Too busy
- ☐ Cannot get time off from work
- ☐ Disability makes it difficult to carry out daily activities
- ☐ Lack of transportation
- ☐ Lack of child care
- ☐ Clinic hours do not fit my schedule
- ☐ Medical insurance coverage issues (no coverage or out-of-pocket cost is too high)
- ☐ Other life issues that come up are more important than an appointment
- ☐ Worried a genetic test result could be used against me (i.e., by employer or for future health insurance, etc.)
- ☐ Clinics are too far away
- ☐ Feeling sick from cancer treatments
- ☐ Too nervous (i.e., don't want to know the risk of inherited cancer)
- ☐ Family members would not want me to go
- ☐ Cultural and/or religious beliefs do not support genetic testing
- ☐ Did not know they existed
- ☐ A doctor told me not to go
- ☐ Other: . . .

(iv) Please tell us why you decided to go for cancer genetics services? (Check all that apply)

- ☐ Benefit my family's future
- ☐ May alter my cancer treatment (preventive surgery, chemotherapy, etc.)
- ☐ Wanted to know my future risk of cancer
- ☐ Already knew someone in my family has a cancer causing gene-change
- ☐ Going seemed very important
- ☐ Family members wanted me to go
- ☐ My doctor recommended that I go
- ☐ Other: . . .

(v) Please tell us what factors made it easier for you to go for cancer genetics services? (Check all that apply)

- ☐ Clinic was close to home
- ☐ Have available transportation
- ☐ Have available childcare

☐ Clinic hours were flexible and fit my schedule

☐ I was able to obtain these services by phone

☐ My medical insurance covered the visit (minimal charge to me)

☐ Other: . . .

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Research Article

Treatment Choices Based on Onco*type*Dx in the Breast Oncology Care Setting

Teri L. Malo,[1] Isaac Lipkus,[2] Tobi Wilson,[3] Hyo S. Han,[4,5] Geza Acs,[4,5,6] and Susan T. Vadaparampil[1,4]

[1] *Health Outcomes and Behavior Program, Division of Cancer Prevention and Control, Moffitt Cancer Center, 12902 Magnolia Drive, MRC-CANCONT, Tampa, FL 33612, USA*
[2] *School of Nursing, Duke University, Medical Center, P.O. Box 3322, Durham, NC 27710, USA*
[3] *Department of Surgery, Feinberg School of Medicine, Northwestern University, 251 East Huron Street Galter 3-150, Chicago, IL 60611, USA*
[4] *Department of Oncologic Sciences, College of Medicine, University of South Florida, 12901 Bruce B. Downs Boulevard, MDC 44, Tampa, FL 33612, USA*
[5] *Department of Women's Oncology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA*
[6] *Department of Anatomic Pathology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA*

Correspondence should be addressed to Susan T. Vadaparampil, susan.vadaparampil@moffitt.org

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Introduction. This study aimed to evaluate whether Onco*type*Dx test results predict receipt of adjuvant chemotherapy in breast cancer patients who received an Onco*type*Dx recurrence score (RS). *Materials and Methods*. Pathology records were used to identify breast cancer patients who had Onco*type*Dx testing between December 2004 and January 2009 ($n = 118$). Patient sociodemographic information, tumor characteristics, RS, and treatment-specific data were collected via chart review. RS was classified as follows: low (RS $\leq$ 17), intermediate (RS = 18–30), or high (RS $\geq$ 31). Bivariate analyses were conducted to investigate the relationship between adjuvant chemotherapy receipt and each sociodemographic and clinical characteristic; significant sociodemographic and clinical variables were included in a multivariable logistic regression model. *Results*. In multivariable analysis controlling for tumor size, histologic grade, and nuclear grade, only RS remained significantly associated with chemotherapy uptake. Relative to low RS, an intermediate (adjusted odds ratio [AOR], 21.24; 95% confidence interval [CI], 3.62–237.52) or high (AOR, 15.07; 95% CI, 1.28–288.21) RS was associated with a greater odds of chemotherapy uptake. *Discussion*. Results indicate that RS was significantly associated with adjuvant chemotherapy uptake, suggesting that Onco*type*Dx results were used to inform treatment decision making, although it is unclear if and how the information was conveyed to patients.

1. Introduction

An estimated 226,870 new cases of breast cancer are expected to be diagnosed in 2012 and account for about 29% of all new cancer cases among US women [1]. Adjuvant chemotherapy is one treatment option for breast cancer patients that is used because of its potential to reduce the risk of breast cancer recurrence and mortality [2]; however, not all patients benefit from adjuvant chemotherapy [3]. Moreover, chemotherapy may be detrimental to quality of life given its potential to produce toxicities, including myelosuppression [2].

The quality of breast cancer care can be improved by informing treatment selection based on individual patient genomic risk profiles [4]; however, to realize the greatest benefits, advances in predictive models that inform treatment decisions must be accepted and used by healthcare providers and patients [5]. One example of predictive modeling that is rapidly moving into the breast oncology care setting is Onco*type*Dx testing [4, 6]. Based on the expression of 21 genes obtained from tumor tissue, Onco*type*Dx testing calculates the risk of breast cancer distant recurrence (i.e., the chance of breast cancer returning as metastatic disease) in patients with estrogen receptor (ER) positive early breast

cancer treated with adjuvant endocrine therapy and predicts the clinical benefit with additional adjuvant chemotherapy. Given that approximately 75% of breast cancers are ER positive and 61% of those cases are lymph node (LN) negative [7], many women with breast cancer may be qualified and benefit from Onco*type*Dx testing.

Although there are clinical guidelines to identify patients who would derive the greatest benefit from Onco*type*Dx testing [6], relatively few studies have been conducted to examine the impact of test results on treatment decisions. Some research has indicated that Onco*type*Dx recurrence score (RS) results have impacted receipt of chemotherapy, including a study of 276 patients who were newly diagnosed with breast cancer between 2005 and 2009 [8]. After controlling for Nottingham Prognostic Index, adjuvant online mortality risk, progesterone receptor (PR) status, and medical oncologists' blinded recommendation for adjuvant chemotherapy, only RS and patient age at diagnosis were significantly associated with receipt of adjuvant chemotherapy. Other studies have linked RS results to changes in adjuvant chemotherapy plans [8–12]. For instance, one study conducted from 2004 to 2006 examined the impact of RS on 29 patients with ER positive and LN negative breast cancer [9]. Results showed that RS changed chemotherapy plans for 9 patients such that 7 of 13 patients for whom chemotherapy was recommended did not receive it, and 2 of 16 patients received chemotherapy after initial recommendations against it.

Though some research has pointed to an association between RS and receipt of adjuvant chemotherapy, currently only one published study collected data beyond 2008 [8]. The current study serves to replicate these findings in another population, with the primary purpose of evaluating whether Onco*type*Dx test results predict receipt of adjuvant chemotherapy in a cohort of consecutive patients with breast cancer who received an Onco*type*Dx RS.

2. Materials and Methods

The study population was comprised of patients treated at Moffitt Cancer Center, a large National Cancer Institute-designated comprehensive cancer center in the southeastern US. Approximately 60% of all patients seen at Moffitt come from the surrounding seven county catchment area, with the remainder of patients coming from other Florida counties, states, and countries. Upon Institutional Review Board approval, Moffitt Cancer Center surgical pathology records were used to identify patients meeting the following criteria (1) diagnosed with breast cancer, and (2) had Onco*type*Dx testing between December 2004 (the year in which the test was approved by the U.S. Food and Drug Administration) and January 2009 (the year in which chart reviews were completed). Based on this information, medical records were reviewed retrospectively to collect patient sociodemographic information, tumor characteristics, Onco*type*Dx RS, and treatment-specific data. Chart abstractions were performed by a study team member after training from the principal investigator. The senior study coordinator reviewed 10% of data files to assess the accuracy of collected data. Finally, a medical oncologist reviewed the summarized data and identified a subset (~10% of charts) for additional review to ensure accuracy.

2.1. Measures. Sociodemographic data included age; marital, parental, and menopause status; race/ethnicity; and family history of breast cancer (present/absent). Clinical characteristics included breast cancer stage; tumor size; LN status; histology; modified combined histologic (Nottingham) grade; nuclear grade; human epidermal growth factor receptor-2 (HER2), ER, PR, and angiolymphatic invasion status; and RS. Regarding RS, patients were classified into one of three groups based on cut points: low (RS $\leq$ 17), intermediate (RS = 18–30), or high (RS $\geq$ 31) [13]. The primary outcome variable, receipt of adjuvant chemotherapy, was based on grouping women into those who had chemotherapy versus those who did not. This comparison was selected as it most closely reflects the primary treatment decision influenced by Onco*type*Dx results [6, 13].

2.2. Data Analyses. Bivariate analyses were used to investigate the relationship between the primary outcome variable, receipt of adjuvant chemotherapy, and the sample sociodemographic and clinical characteristics. Pearson Chi-square or Fisher's Exact tests were used to study relationships with each categorical variable of interest; a t-test was conducted to examine differences in age and RS by chemotherapy uptake group. Analyses used two-tailed tests of significance with the significance level set at $P < 0.05$.

In an effort to maintain an acceptable case-to-variable ratio, independent variables included in the final multivariable logistic regression model were selected based on variables significant in the bivariate analyses. Odds ratios (OR) and their 95% confidence interval (CI) were estimated from the logistic regression model. Given the variables' small expected cell counts, an exact analysis was conducted. Analyses were performed using the SAS 9.1 statistical software package (SAS Institute Inc, Cary, North Carolina).

3. Results

Chemotherapy status was unknown for 8 patients; data for the remaining 118 patients were used for analyses. Patient demographic and clinical characteristics are presented in Table 1. Patients' mean age was 56.3 years (SD = 11.0; range: 33–84). Most participants were married or living with a partner (70.3%), White (84.8%), had children (72.0%), and were perimenopausal/postmenopausal (63.6%). Just over half (52.5%) had no family history of breast cancer.

Most patients had stage I breast cancer (80.5%), a tumor size >1.0 cm (78.8%), and were LN negative (95.8%). The majority (84.8%) had invasive ductal carcinoma (IDC), and over half (56.8%) of the tumors showed intermediate histologic grade. The largest proportion of patients had a nuclear grade of 2 (47.5%). Most patients' tumors were HER2 negative (94.9%), ER positive (99.2%), PR positive (89.0%),

Table 1

(a) Patient demographic and clinical characteristics by chemotherapy group ($N = 118$)[a]

Characteristics	Total ($N = 118$) n (%)	Chemotherapy Yes ($n = 35$) n (%)	Chemotherapy No ($n = 83$) n (%)	P[b]
Demographic				
Age in years mean (SD)	56.3 (11.0)	54.1 (10.4)	57.3 (11.1)	.1513
Marital status				.0968
Married/living with partner	83 (70.3)	28 (80.0)	55 (66.3)	
Other	33 (28.0)	6 (17.1)	27 (32.5)	
Parental status				.6933
Children	85 (72.0)	24 (68.6)	61 (73.5)	
No children	28 (23.7)	9 (25.7)	19 (22.9)	
Menopause status				.2037
Premenopause	38 (32.2)	14 (40.0)	24 (28.9)	
Perimenopause/postmenopause	75 (63.6)	19 (54.3)	56 (67.5)	
Race/ethnicity				.6003
White	100 (84.8)	29 (82.9)	71 (85.5)	
Other	17 (14.4)	6 (17.1)	11 (13.3)	
Family history				.5314
Absent	62 (52.5)	17 (48.6)	45 (54.2)	
Present	55 (46.6)	18 (51.4)	37 (44.6)	
Clinical				
Breast cancer stage				.0595
I	95 (80.5)	25 (71.4)	70 (84.3)	
II A	19 (16.1)	8 (22.9)	11 (13.3)	
II B	2 (1.7)	0 (0.0)	2 (2.4)	
III/III B	2 (1.7)	2 (5.7)	0 (0.0)	
Tumor size (mean in cm)	1.6	1.8	1.5	.0694
≤.5 cm	3 (2.5)	1 (2.9)	2 (2.4)	.0462*
0.6–1.0 cm	22 (18.6)	2 (5.7)	20 (24.1)	
>1.0 cm	93 (78.8)	32 (91.4)	61 (73.5)	
Lymph node				1.0000
Positive	4 (3.4)	1 (2.9)	3 (3.6)	
Negative	113 (95.8)	34 (97.1)	79 (95.2)	
Histology				.1542
IDC	100 (84.8)	33 (94.3)	67 (80.7)	
ILC	7 (5.9)	2 (5.7)	5 (6.0)	
Mixed	9 (7.6)	0 (0.0)	9 (10.8)	
Other	2 (1.7)	0 (0.0)	2 (2.4)	
Histologic grade				.0160*
Low	33 (28.0)	7 (20.0)	26 (31.3)	
Intermediate	67 (56.8)	18 (51.4)	49 (59.0)	
High	17 (14.4)	10 (28.6)	7 (8.4)	

(b) Patient demographic and clinical characteristics by chemotherapy group

Characteristics	Total ($N = 118$)	Chemotherapy Yes ($n = 35$)	Chemotherapy No ($n = 83$)	P[a]
Nuclear grade				.0004*
1	6 (5.1)	1 (2.9)	5 (6.0)	
2	56 (47.5)	8 (22.9)	48 (57.8)	
3	24 (20.3)	14 (40.0)	10 (12.1)	

(b) Continued.

Characteristics	Total ($N = 118$)	Chemotherapy		P^a
		Yes ($n = 35$)	No ($n = 83$)	
HER2				.3598
Positive	6 (5.1)	3 (8.6)	3 (3.6)	
Negative	112 (94.9)	32 (91.4)	80 (96.4)	
ER				.2966
Positive	117 (99.2)	34 (97.1)	83 (100.0)	
Negative	1 (0.9)	1 (2.9)	0 (0.0)	
PR				.0560
Positive	105 (89.0)	28 (80.0)	77 (92.8)	
Negative	13 (11.0)	7 (20.0)	6 (7.2)	
Angiolymphatic invasion				.1092
Absent	86 (72.9)	23 (65.7)	63 (75.9)	
Present	20 (17.0)	9 (25.7)	11 (13.3)	
Recurrence score (mean)	19.0	26.4	15.9	<.0001*
Low	68 (57.6)	4 (11.4)	64 (77.1)	<.0001*
Intermediate	37 (31.4)	24 (68.6)	13 (15.7)	
High	13 (11.0)	7 (20.0)	6 (7.2)	

[a]Percentages may not total 100 as a result of rounding or missing data, or both.
[b]A chi-square or Fisher's exact test was used for categorical variables, and an independent samples t-test was used to compare means for the age, tumor size, and recurrence risk score variables.

and did not show angiolymphatic invasion (72.9%). The mean RS was 19.0 and the largest proportion of patients had a low RS (57.6%).

In bivariate analyses, tumor size, histologic grade, nuclear grade, and RS were significantly associated with uptake of adjuvant chemotherapy (Table 1). Compared to patients who did not receive chemotherapy, those who received chemotherapy had a greater proportion of tumor size >1.0 cm (91.4% versus 73.5%), high histologic grade (28.6% versus 8.4%), nuclear grade of 3 (40.0% versus 12.1%), intermediate (68.6% versus 15.7%) and high (20.0% versus 7.2%) RS category, and higher mean RS (26.4 versus 15.9). In multivariable analysis controlling for tumor size, histologic grade, and nuclear grade, only RS remained statistically significantly associated with chemotherapy receipt (Table 2). Relative to those with a low RS, those with an intermediate (adjusted odds ratio [AOR], 21.24; 95% CI, 3.62–237.52) or high (AOR, 15.07; 95% CI, 1.28–288.21) RS had a greater odds of chemotherapy uptake.

Table 2: Logistic regression for uptake of adjuvant chemotherapy ($n = 85$).

Variable	Adjusted odds ratio (95% confidence interval)
Tumor size	
≤.5 cm	Reference
0.6–1.0 cm	0.21 (0.00–32.74)
>1.0 cm	1.24 (0.03–138.62)
Histologic grade	
Low	Reference
Intermediate	0.62 (0.05–8.16)
High	0.33 (0.01–9.71)
Nuclear grade	
1	Reference
2	0.74 (0.01–122.90)
3	2.42 (0.02–563.30)
Recurrence score*	
Low	Reference
Intermediate	21.24 (3.62–237.52)
High	15.07 (1.28–288.21)

*$P < .05$.

4. Discussion

Study results indicate that RS was significantly associated with adjuvant chemotherapy uptake, suggesting that in our sample of female breast cancer patients who underwent Onco*type*Dx testing, the results of this gene assay were likely being used to inform treatment decision making, although it is unclear if and how the information was conveyed to patients. RS score was a significant predictor of chemotherapy uptake after controlling for more standard clinicopathological markers used to guide treatment selection, specifically tumor size, LN status, histologic grade, and nuclear grade. These results are consistent with earlier research that has shown that RS was associated with whether patients received adjuvant chemotherapy or not [8–12].

Adjuvant chemotherapy is recommended for individuals with RS scores in the high-risk category, whereas it is unlikely to benefit individuals in the low-risk category [13, 14].

In our study, patients with a low RS were least likely to receive adjuvant chemotherapy (94% of low-risk patients did not receive chemotherapy). This finding is consistent with research showing that RS affects treatment decision-making for low-risk patients [15] and is similar to the Ademuyiwa study [8], which reported that 91% of patients with a low RS did not receive chemotherapy.

Although National Comprehensive Cancer Network guidelines recommend chemotherapy for individuals with high RS, in our patient population, only 54% of individuals with high RS received chemotherapy. This percentage is lower than that of the Ademuyiwa study [8], which reported that 96% of patients with high RS received chemotherapy. For our sample of patients in these higher risk categories, the receipt of chemotherapy is likely multifactorial (based on coexisting clinicopathological features). Due to the small sample sizes in this study, we were unable to more fully investigate the patterns of treatment choice based on these multiple factors.

Of interest was the finding that one ER negative patient and four LN positive patients received an RS, even though the test has been validated for ER positive and LN negative breast cancer patients at the time Onco*type*Dx testing was performed. The ER negative patient was HER2 negative and T1cN0. All LN positive patients were HER2 negative with primary tumor categories ranging from one to four. Additionally, there were six HER2 positive patients who received an RS, one of whom was T1aN0, four were T1bN0, and one was T1cN0. It is possible that the RS was felt to be of utility for these patients, and perceived as an additional measure of breast cancer recurrence risk to support a decision about adjuvant chemotherapy, as was noted in one patient chart.

Most of the published literature regarding the use of RS to guide treatment selection focuses on physicians' use of this information in guiding treatment selection [8, 10], with limited evaluation of the patient's role in the decision to pursue a therapy. Factors that patients may consider in their treatment decisions include side effects that can adversely affect quality of life, patient preference for participation in treatment decision-making, and understanding of the results; the latter may be particularly critical where greatest uncertainty exists, that is, for patients with an intermediate RS. A preference for an active role in decision-making among those presented with Onco*type*Dx results is related to health literacy, such that women with high-health literacy prefer a more active role in decision-making, whereas low-health literacy is related to preference for more shared and passive decision-making [16]. Our group recently completed a retrospective cross-sectional survey of a subset of the patients ($n = 64$) included in the present study and found that women incorrectly answered approximately half of a series of 14 items evaluating knowledge about RS [17]. Another similarly designed study of 77 breast cancer patients found that one-third of participants did not fully understand discussions related to RS [18]. Although not a focus of this study, it would be of interest to investigate how these variables interact to guide treatment planning for patients in the higher-risk RS categories.

To date, much of the research on Onco*type*Dx results' association with treatment decision-making has occurred in an academic setting. Some research conducted with an inner-city population suggests that Onco*type*Dx results may influence chemotherapy treatment decisions in this setting [19]. In this sample of 47 women who underwent Onco*type*Dx testing, 5% of women with a low RS and 100% of women with a high RS received chemotherapy. The results for women with a low RS are aligned with the current study and Ademuyiwa study [8], and results for women with a high RS are similar to the Ademuyiwa study. More research needs to be conducted with larger samples of women from populations outside of the academic setting.

This study has several limitations. First, the confidence intervals for the RS categories were wide, thus estimates may be imprecise. This is likely an effect of the relatively small sample size. Second, although several clinicopathological and demographic variables were included in the study, the small sample sizes limited our ability to further elucidate trends among individuals in the higher-risk RS categories who did not receive adjuvant chemotherapy. Third, family history was recorded in the patient's chart based on patient self-report and, like other self-report data, may be inaccurate; however, some research on the concordance between self-report of family breast cancer history and cancer confirmation sources (e.g., state tumor registry) suggests a sensitivity ranging from 61% to 95% [20, 21]. Fourth, as the study was retrospective, we were unable to assess definitively whether treatment planning was changed as a result of the availability of the RS score and whether patients themselves were able to use the RS to aid their treatment decision. Also, we did not account for the possible role that comorbidity may have played in the uptake of chemotherapy. Given that higher comorbidity has been linked to a decreased likelihood of receiving chemotherapy among women aged 55 and older [22], it is possible that comorbid conditions may also have been associated with chemotherapy among older women in the current study. Another limitation is the relatively heterogenous population with regard to race/ethnicity. Although reflective of the patient population at this institution, findings may not be generalizable to other races and ethnicities. Finally, some patients may have received chemotherapy after the data collection period ended and this change in chemotherapy receipt status was not reflected in the analyses.

In summary, the current study offers relatively recent data to support results of previous research documenting a change in treatment selection based on the use of the RS [8–12]. The literature remains in need of studies investigating the variables associated with a patient's use of this valuable health information, including the potential role of comorbidities, as well as studies conducted with populations outside of the academic setting. This paper has important implications for prevention, such that women with a lower risk of breast cancer recurrence as determined by Onco*type*Dx testing may be able to avoid the potential toxicity associated with chemotherapy.

Conflict of Interests

Regarding potential conflict of interests, Dr. Acs serves on the Speakers' Bureau for Genomic Health, Inc. and Clarient, Inc. The other authors report no conflicts.

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Research Article

Psychosocial and Quality of Life in Women Receiving the 21-Gene Recurrence Score Assay: The Impact of Decision Style in Women with Intermediate RS

Nadiyah Sulayman, Elizabeth Spellman, Kristi D. Graves, Beth N. Peshkin, Claudine Isaacs, Marc D. Schwartz, and Suzanne C. O'Neill

Department of Oncology, The Fisher Center for Familial Cancer Research, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3300 Whitehaven Street, NW, Suite 4100, Washington, DC 20007, USA

Correspondence should be addressed to Suzanne C. O'Neill, sco4@georgetown.edu

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Multigene assays such as the 21-gene recurrence score (RS) quantify risk for recurrence and potential benefit from chemotherapy in early-stage, ER+ breast cancers. Few studies have assessed the impact of testing on patient-reported outcomes such as cancer-related distress or quality of life. The few studies that have assessed these outcomes do not consider potential modifiers, such as the patients' level of involvement in the treatment decision-making process. In the current study, 81 breast cancer patients who received the RS assay completed cross-sectional surveys. We used linear multiple regression to assess whether test result, decision-making role (passive versus shared/active), and their interaction contributed to current levels of distress, quality of life, and decisional conflict. There were no associations between these variables and test result or decision-making role. However, women who received an intermediate RS and took a passive role in their care reported higher-cancer-related distress and cancer worry and lower quality of life than those who took a shared or active role. These data should be confirmed in prospective samples, as these poorer outcomes could be amenable to intervention.

1. Introduction

Improvements in our understanding of the molecular mechanisms of breast cancer progression, diagnosis, and treatment represent a major advance [1]. Genomic profiling of breast tumors increasingly is being used clinically to refine recurrence estimates and guide adjuvant treatment decisions in early-stage, hormone-receptor positive breast cancer [2] and has been integrated into clinical guidelines for this group of patients [3, 4]. The 21-gene recurrence score (RS) assay (Onco*type* DX; Genomic Health Inc., Redwood City, CA) quantifies risk of recurrence in patients with early stage, estrogen-receptor- (ER-) positive breast cancer treated with tamoxifen. While data have accumulated to support treatment recommendations for the 25% of women who receive high RS and 50% who receive low RS, [5, 6] recommendations for the remaining quarter of patients with intermediate RS remain less clear pending additional trials, presenting a clinical challenge [7]. Like other cancer treatment decisions which involve more than one appropriate treatment option [8, 9], the uncertainty related to this clinical equipoise could require patients to take more active roles in their treatment decision-making than those who receive a high or low RS.

Several studies demonstrate that the RS impacts treatment decisions for physicians and patients [10–14]. Specifically, RS information changes oncologists' chemotherapy treatment recommendations in 25%–44% of cases [11, 13, 15], usually from combined chemohormonal therapy to hormone therapy alone [10, 11, 16]. However, few studies demonstrate how the RS relates to patient decision-making processes or patient-reported psychosocial and quality of life outcomes. Lo et al. [17] reported that decisional conflict and anxiety decline in the year after receipt of the RS and that quality of life remains stable [17], but they did

not assess whether outcomes vary by test result or patient-related factors. Previous research demonstrates that many women who receive their RS do not take part in the treatment decision-making process as they would prefer [18, 19]. While meeting these decision role preferences has been linked to improved patient outcomes [20, 21], breast cancer patients who take a passive role in treatment decision-making report lower quality of life and higher distress than women who take an active or shared role, regardless of their preferred decision-making role [22–24]. Therefore, patient involvement in how the RS informs adjuvant care decisions could relate to differential psychosocial and quality-of-life outcomes among tested women. Active or shared involvement with treatment decision-making may be most appropriate in clinical circumstances in which evidence is either incomplete or suggests more than one option could be appropriate [25, 26]. While breast cancer treatment decisions often involve multiple options and decision points, in the context of the Onco*type* RS, active or shared decision making may be particularly salient for women who receive an intermediate RS given the current absence of standard treatment recommendations for this group.

In the present study, we retrospectively evaluated the effect of RS category (i.e., low, intermediate, high RS), decision-making style, and their interaction on patient-reported distress, decisional conflict and quality of life in women who had received testing at the time of their diagnosis. We predicted that (1) women who preferred a passive decision-making style would report higher distress and decisional conflict and lower quality of life than women who took an active or shared role in their care and (2) these effects would be stronger in women who had intermediate RS than in women with high or low RS.

2. Methods

2.1. Study Population. Female participants were recruited from 2009-2010 and had been treated at Lombardi Comprehensive Cancer Center from 2005–2009. We identified patients who had received testing through pathology record systems that track all tests ordered at Lombardi. Eligibility included having been tested with the 21-gene RS test, having completed chemotherapy treatment, and not having a recurrence of their primary breast cancer or a second cancer. In addition, participants could not have other major comorbid disease or participate in clinical trials that could have impacted treatment decision making among women with an RS, as these circumstances would have removed the treatment decision from the patient and their physician. Only women with valid contact information were considered eligible. The study was approved by the Institutional Review Board of Georgetown University. All participants provided written informed consent.

Eligible women received a mailed survey, consent and HIPAA documents, a letter of invitation from their attending physician, and a self-addressed stamped envelope in which to return the study documents. They also received a self-addressed stamped postcard by which they could indicate their interest in declining the study. We identified 128 potentially eligible women diagnosed with early-stage, ER+ breast cancer who had received the 21-gene RS test results confirmed via chart review. Of these, 46 (36%) refused participation (17 active and 29 passive refusals); 1 returned her questionnaire without a signed consent form and did not respond to requests to complete the consent. Thus, our final sample of 81 women who received testing and completed questionnaires and consents represents 63% of the eligible sample (Figure 1). While we were unable to obtain clinical characteristics from women who refused participation, our final sample was similar in race/ethnicity to our clinic population (70% white).

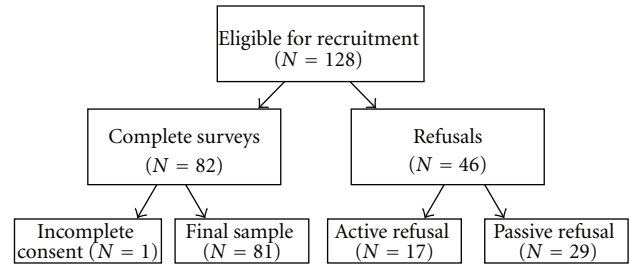

Figure 1: Participant recruitment and enrollment.

2.2. Measures

2.2.1. Participants' Characteristics. We assessed age, education, race, marital, and financial status. A trained research assistant performed chart reviews to obtain the following: RS, tumor stage and grade, receptor status, primary therapy, and adjuvant therapy. We computed participants' 10-year risk for recurrence using a validated tool (Adjuvant! Online) that provides a quantitative risk estimate using clinical parameters [27, 28]. In addition to chart review, we also assessed RS and treatments received via self-report. Given that all patients were recruited during the clinical trial to determine treatment recommendations for women with intermediate RS (TailoRx), we categorized RS using the trial guidelines: low (<11), intermediate (11–25), and high (>25).

2.2.2. Decision Style. We used the Control Preferences Scale [29, 30] to assess patients' preferences for shared medical decision making. The scale is composed of five statements which are separated into passive "*I preferred that my doctor make the decision about treatment; I preferred that my doctor make the decision about treatment, but strongly considers my opinion,*" shared "*I preferred that my doctor and I make the decision about treatment together on an equal basis*" and active "*I preferred that I make the decision about treatment, but strongly consider the doctor's opinion; I preferred that I make the decision about treatment*" decision styles. Patients were asked "which of these best describes your way of making a decision about your cancer treatment?"

2.2.3. Cancer-Related Distress. We used the 15-item Impact of Event Scale (IES) [31] to measure cancer-specific distress. The IES measures intrusive and avoidant thoughts/behaviors

associated with a specific stressor. Items are scored on a 4-point scale (*not at all-often*), indicating how frequently each thought/behavior occurred during the past seven days in regards to their cancer diagnosis. This scale had excellent internal consistency ($\alpha = .93$). A score greater than 19 indicates high distress [31].

2.2.4. Cancer Worry. We assessed how often the participant worried about her risk of recurrence during the past two weeks, measured on a 4-point Likert scale *(not at all-all of the time)* [32].

2.2.5. Quality of Life. We measured quality of life with the FACT-B [33], a well-validated and frequently used measure of health-related quality of life in patients with breast cancer. It consists of the FACT-General (FACT-G) and the 9-item Breast Cancer Subscale. Patients indicated how true each statement was for them in the past seven days measured on a 5-point Likert scale (0 = *not at all* to 4 = *very much*), with higher scores indicating better quality of life. This scale demonstrated excellent internal consistency ($\alpha = .92$).

2.2.6. Decisional Conflict. We assessed decisional conflict with the Decisional Conflict Scale (DCS) [34], which consists of 16 items measured on a 5-point Likert scale (1 = *strongly agree* to 5 = *strongly disagree*). Patients were asked to think about the choice they had made about their breast cancer treatment. The DCS measures uncertainty about the decision (3 items), feeling uninformed about the decision (3 items), feeling unsupported in decision making (3 items), feeling unclear about values (3 items), and the perceived quality of the decision (4 items). Items were averaged so that higher scores indicated higher decisional conflict. The measure demonstrated good internal reliability ($\alpha = .89$). A score of 2 or above is considered high decisional conflict.

2.3. Data Analysis. We calculated descriptive statistics for all sociodemographic, treatment-related, psychosocial, and quality of life variables. We assessed bivariate associations between sociodemographics and treatment-related variables, as well as psychosocial, and quality of life outcomes. In multivariate analyses, we adjusted for all variables with bivariate associations of $P < .10$. We used multiple linear regression with hierarchical variable entry, entering covariates on Step 1, decision style on Step 2, RS category on Step 3, and their interaction in the final step. Data were analyzed using SPSS 19.0. With a sample of 81 participants, we were powered to find effects of .17 for our main effects and .26 for our interaction effects.

3. Results

3.1. Participant Characteristics. Mean scores and percentages are shown in Table 1. Participants were, on average, 19 months from diagnosis and testing (range = 6–64 months). All women who received high or low RS results received result-concordant treatment, with higher risk patients receiving chemohormonal therapy and lower risk patients receiving hormonal therapy only. Among patients with intermediate RS, 38 (75%) received hormonal therapy only and 13 (25%) received combined therapy. The latter group had marginally higher risk according to Adjuvant! scores (26.6 versus 22.3, $t(44) = 1.72$, $P = .09$). Most women indicated that they preferred a shared (36%) or active (49%) decision-making style in their treatment for breast cancer. The only sociodemographic or treatment variable related to our outcomes was race. White women had significantly higher cancer worry ($t(79) = 2.05$, $P = .04$) and lower quality of life ($t(79) = -2.00$, $P = .05$) compared to others. We adjusted for race in subsequent models. Importantly, neither time since diagnosis nor receipt of chemotherapy was related to any of our outcomes.

3.2. Levels of Distress, Decisional Conflict, and Quality of Life. Women reported moderate levels of cancer-related distress ($M = 19.10$, SD = 17.50), cancer worry ($M = 1.70$, SD = 0.80), and decisional conflict ($M = 1.70$, SD = 0.50). Though overall values indicate adequate global functioning in this sample, 30% of women reported problematic levels of decisional conflict (scores ≥ 2) and 38.7% of women reported high levels of cancer-related distress (scores > 19) [35].

3.3. Association of Decision Style and RS with Distress and Decisional Conflict. We conducted separate hierarchical multiple regression analyses for cancer-related distress, worry about recurrence, and decisional conflict. After controlling for race on Step 1, we entered decision style on Step 2, RS category (intermediate versus low/high) on Step 3, and their interaction in the final step (Table 2). Neither decision style on Step 2 nor RS categories on Step 3 were associated with cancer-related distress or worry about recurrence. However, in the final model on Step 4, the interaction between decision style and RS was associated with cancer-related distress ($\Delta R^2 = .12$, $P = .002$) and worry about recurrence ($\Delta R^2 = .05$, $P = .04$). We further assessed these significant interactions with simple effects analysis. As displayed in Figure 2, among women who preferred an active/shared role in their care, RS was unrelated to cancer-related distress. However, among women who preferred a passive role, results were poorer for women with intermediate RS than high/low RS. Specifically, among women with an intermediate RS, a passive versus shared/active decision style was related to higher cancer-related distress (38.20 versus 17.40; $t(49) = 2.75$, $P = .008$). This simple effects analysis was not significant for worry about recurrence (1.70 versus 1.60, $t(49) = .30$, $P = .77$). In our model for decisional conflict, those who preferred a passive decision style reported significantly higher decisional conflict on Step 2 ($\Delta R^2 = .06$, $P = .03$). However, this was not significant in the final model. Neither RS nor the decision style x RS interaction was significantly associated with decisional conflict.

3.4. Association of Decision Style and RS with Quality of Life. We also tested the association between decision style, test result, and their interaction on quality of life. Neither decision style on Step 2 nor RS categories on Step 3 were

Table 1: Sociodemographic and medical characteristics ($N = 81$).

Sociodemographics	N (%)	M (SD)
Age		54.35 (9.18)
Education		
<College degree	22 (27)	
College degree	19 (23)	
Graduate/professional training	40 (50)	
Race		
Caucasian	62 (77)	
Non-Caucasian	19 (23)	
Marital status		
Married/partner	50 (62)	
Single/widow/divorced	31 (38)	
Annual household income		
< $50,000	14 (17)	
$50,000–100,000	10 (12)	
> $100,000	45 (56)	
Refused/missing	12 (15)	
Treatments received		
Surgery		
Lumpectomy	48 (59)	
Unilateral mastectomy	17 (21)	
Bilateral mastectomy	16 (20)	
Chemotherapy		
Yes	24 (30)	
No	57 (70)	
Radiation		
Yes	24 (30)	
No	57 (70)	
Tamoxifen		
Yes	47 (58)	
No	34 (42)	
Aromatase inhibitors		
Yes	32 (40)	
No	48 (59)	
Do not know	1 (1)	
Recurrence Score × Treatment		
Low-hormonal therapy	19 (23)	
Intermediate-hormonal therapy	38 (47)	
Intermediate-chemohormonal therapy	13 (16)	
High-chemohormonal therapy	11 (14)	
Psychosocial and quality of life variables		
Decision style		
Passive	12 (15)	
Shared	29 (36)	
Active	40 (49)	
Cancer-related distress (IES)		19.06 (17.51)
Decisional conflict		1.69 (.51)
Worry about recurrence		1.65 (.83)
Quality of life (FACT-B)		111.75 (18.85)

Table 2: Multivariate regression analysis of relationship between decision style, RS, and patient-reported outcomes.

	FACT-B			IES			DCS			Cancer worry		
	ΔR^2	ΔF	Final β	ΔR^2	ΔF	Final β	ΔR^2	ΔF	Final β	ΔR^2	ΔF	Final β
Race	0.04	3.03	−0.20	0.02	1.86	0.17	0.02	1.84	0.11	0.05	4.06*	0.27*
Decision style[1]	0.02	1.25	−0.31*	0.01	0.67	0.40**	0.06	4.66*	0.25	0.02	1.93	0.02
RS test result[2]	0.01	0.06	−0.13	0.01	0.35	0.08	0.01	0.45	−0.07	0.01	0.30	0.16
Decision style × test result	0.05	4.14*	0.31*	0.12	10.49**	−0.49**	0.00	0.01	−0.01	0.05	4.23*	−0.31*

[1]Passive versus shared/active. [2]Intermediate RS versus high/low RS.
*$P < .05$; **$P < .01$.

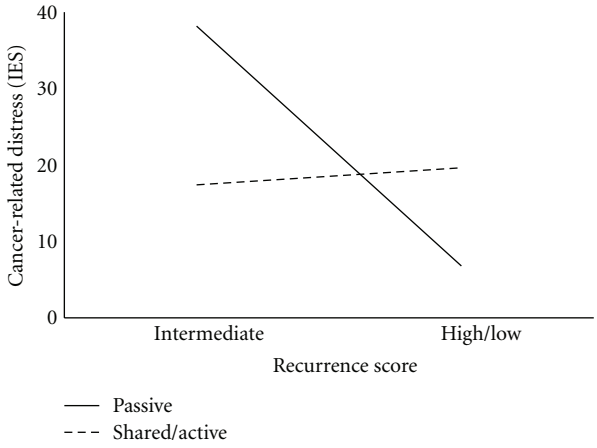

Figure 2: Cancer-related distress (IES) by RS (intermediate versus high/low) and decision style (passive versus shared/active).

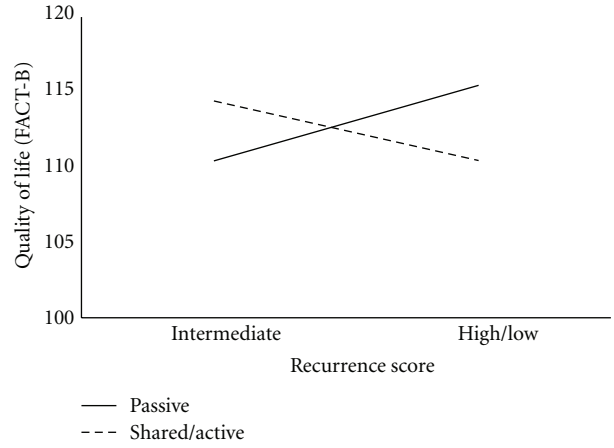

Figure 3: Quality of life (FACT-B) by RS (intermediate versus high/low) and decision style (passive versus shared/active).

associated with quality of life. However, on Step 4, the interaction between decision style and RS was associated with quality of life ($\Delta R^2 = .05$, $P = .04$). Again, our simple effects analysis demonstrated that while there were no significant differences among women who preferred an active/shared role in their care, among women who preferred a passive role, those with intermediate RS reported poorer quality of life than those high/low RS (Figure 3). Specifically, among women with an intermediate RS, those who preferred a passive role in their care reported significantly lower quality of life than those who took an active/shared role (97.60 versus 114.40; $t(49) = -2.27$, $P = .03$).

4. Discussion

The 21-gene RS impacts adjuvant treatment decisions of patients and their providers [10–14]. In the present study, we found that women who receive their RS have levels of quality of life and distress comparable to other women who are a year or more from being diagnosed and treated for early-stage breast cancer and make RS-congruent treatment decisions [17, 36, 37]. Further, we found no evidence that these associations vary based on the risk of recurrence indicated by the RS or the treatment received. However, in this sample of tested women, a passive decision role preference was associated with higher distress and lower quality of life. This is especially true for women who received an intermediate RS. In addition, like the broader population of women diagnosed with breast cancer, a substantial number—more than one-third—of women continue to experience significant distress, even a year or more after diagnosis.

The present study extends prior results by demonstrating that while women who receive RS testing, as a whole, do well, there is significant variability in outcomes as a result of both test result received and the level of involvement these women take in their treatment decisions. Indeed, 40% of the sample reported problematic levels of cancer-related distress, a substantial number considering these women were several months removed from their active treatment. This is similar to previous work on women who receive *BRCA1/2* mutation testing. Several systematic reviews demonstrate that, as a whole, genetic counseling and testing for breast cancer susceptibility do not result in significant psychological distress or decrements in quality of life for this population of patients as a whole [38–40]. However, an extensive literature, including our own work, demonstrates that some women, such as those with high pretesting distress, a significant family history of the disease, a high expectation for carrying a deleterious mutation, and difficulty with uncertain health information, are at risk for long-term distress [37, 41]. Similarly, most women who receive their RS may adjust well, but a subgroup of women may be at risk for poorer outcomes and in need of additional support. This question deserves additional research in larger, more representative samples.

Long-standing trends in health care call for patients to be more involved in their care [42]. Patient involvement and

integration with treatment decision making may be most appropriate in clinical circumstances in which evidence is either incomplete or suggests more than one option could be appropriate [25, 26]. Previous studies of women with breast cancer show that quality of life and satisfaction are associated with active or shared involvement in care decisions [21, 23, 43, 44]. The clinical equipoise and uncertainties associated with an intermediate RS could mean that treatment decisions rely more on women's treatment-related values and preferences in combination with standard clinical criteria and the physician's clinical judgment. Importantly, the receipt of chemotherapy among women with intermediate RS was marginally associated with the patient's Adjuvant! Online score, suggesting that clinical factors are an important part, but not the only consideration, in treatment decisions. This underscores the multifaceted nature of treatment decisions in women with intermediate RS at this time [7].

The uncertainties associated with intermediate RS could make the need for active or shared decision making more apparent. Genomic medicine often makes the uncertainties that are ever-present in medical decisions more obvious to patients, as risks often are communicated as probabilities and on continua [8, 45]. The intermediate RS is one prominent example of this, but it is not the only one and there are likely to be many others. How patients and providers communicate about these uncertainties and come to treatment decisions will likely impact the benefit that patients ultimately will gain from these new technologies. Women in this group may benefit from decision support interventions aimed at fostering shared decision making and providing the tools to do so [46, 47] or interventions to promote coping and reduce distress in the face of clinical uncertainty. Interestingly, despite 30% of our sample indicating problematic levels of decisional conflict, neither test result, decision style nor their interaction was associated with this variable. Our cross-sectional data do not allow us to determine whether these null findings are a result of being removed in time from the treatment decision, measurement issues, or another explanation. Future prospective, longitudinal research should examine this issue and how it would influence the development of interventions for this population.

This study has several limitations, including a retrospective, cross-sectional design and a relatively small sample limited to women who had completed treatment for breast cancer. Specifically, participants may not accurately remember their decision role preference. However, previous research has found strong associations between these retrospective perceptions and those measured at the time of care [48] and retrospective methods are used frequently in cancer decision-making research [49, 50]. Future research should follow women prospectively from the time of diagnosis and RS testing. Ideally, this would occur before they receive their RS results and make definite treatment decisions in order to prospectively assess the impact of the testing and treatment decision making process on long-term patient-reported outcomes. We were also limited by lack of an untested control group to which to compare our outcomes. At the time the study was implemented, testing had become the standard of care, limiting the ability to make this comparison [4]. Another limitation includes our use of a single site at a comprehensive cancer center and a patient population with a relatively high self-reported income. The patient population and clinical encounters captured in the current study may not fully reflect those in other settings. This could also be impacted by our relatively low response rate. Our use of a mailed survey as a means of recruitment may also have resulted in a lower rate of recruitment than if we have been able to recruit women in person. Finally, all of the women in the study had lymph node-negative disease. As testing becomes more common among women with limited node involvement [51, 52], the need for greater active or shared decision making for these women may expand as well.

In conclusion, this study underscores the important role that patient decision-making style plays for women who receive RS as part of their diagnosis and treatment process. This is particularly true for those with intermediate RS. These results hold greater uncertainty, and consequently, might require more input from patients to clarify the values and preferences they hold regarding their care. Our results should be replicated in larger, prospective, multicenter study of women who have received this testing. Future research also should determine the best means to assist these patients in participating in their care decisions.

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Research Article

Increasing Public Awareness of Direct-to-Consumer Genetic Tests: Health Care Access, Internet Use, and Population Density Correlates

Lila J. Finney Rutten,[1] Sarah E. Gollust,[2] Sana Naveed,[3] and Richard P. Moser[3]

[1] *Clinical Monitoring Research Program, SAIC-Frederick, Inc., NCI, Frederick, MD 21702, USA*
[2] *Division of Health Policy and Management, University of Minnesota, 420 Delaware Street SE, MMC 729, Minneapolis, MN 55455, USA*
[3] *Division of Cancer Control and Population Sciences, National Cancer Institute, 6130 Executive Boulvard, MSC 7326, Bethesda, MD 20892, USA*

Correspondence should be addressed to Lila J. Finney Rutten, finneyl@mail.nih.gov

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Uncertainty around the value of and appropriate regulatory models for direct-to-consumer (DTC) genetic testing underscores the importance of tracking public awareness of these services. We analyzed nationally representative, cross-sectional data from the Health Information National Trends Survey in 2008 ($n = 7,674$) and 2011 ($n = 3,959$) to assess population-level changes in awareness of DTC genetic testing in the U.S. and to explore sociodemographic, health care, Internet use, and population density correlates. Overall, awareness increased significantly from 29% in 2008 to 37% in 2011. The observed increase in awareness from 2008 to 2011 remained significant (OR = 1.39) even when adjusted for sociodemographic variables, health care access, Internet use, and population density. Independent of survey year, the odds of awareness of DTC genetic tests were significantly higher for those aged 50–64 (OR = 1.64), and 65–74 (OR = 1.60); college graduates (OR = 2.02); those with a regular source of health care (OR = 1.27); those with a prior cancer diagnosis (OR = 1.24); those who use the Internet (OR = 1.27); and those living in urban areas (OR = 1.25). Surveillance of awareness—along with empirical data on use of and response to genetic risk information—can inform public health and policy efforts to maximize benefits and minimize risks of DTC genetic testing.

1. Introduction

Ongoing genetic discoveries and technological innovation during the past decade have appreciably expanded the availability of genetic tests related to health conditions. Concomitant with the advancement of genetic science has been the development of two trends, the marketing of genetic tests directly to consumers (i.e., through paid advertisements in print media, television, and the Internet) and the direct availability of genetic tests to consumers (i.e., through the Internet) [1]. Regarding the latter, consumers can purchase genetic tests, often without involving their health care provider, that indicate personal risk for conditions ranging from trivial characteristics (e.g., earwax type) to serious health conditions (e.g., breast cancer, Alzheimer's disease) [1–3].

Both the direct marketing of genetic tests and their direct-to-consumer (DTC) availability have been controversial [4], with an increasing volume of health scholarship devoted to the topic [1, 2, 4–10]. While proponents of DTC tests argue that individuals should have the right to access their genetic information in a private setting (without going through the traditional health care setting), critics argue that DTC genetic testing has significant risks, both to the individuals and to the health care system [1, 2, 4, 6–10].

Since 2010, several regulatory actions have been taken in the United States with regard to DTC genetic testing, including letters to companies by the Food and Drug

Administration and reports produced by the Government Accountability Office [3]. A fully informed policy analysis of the benefits and potential harms of DTC genetic testing is impossible without understanding the extent of consumer demand for, use of, and psychosocial and behavioral response to these services [2, 3, 6, 11–13]. Awareness of DTC services is a necessary precursor to demand, as consumers (with rare exceptions, as when services are purchased as a gift) must be aware of the existence of these services before pursuing them. A systematic population-level assessment of awareness of DTC services reveals the extent of public interest in these services and the reach of marketing, which can help policymakers predict whether the risks and benefits of DTC genetic testing will be confined to a narrow subpopulation of consumers or is a more widespread population concern. Prior research examining awareness of DTC genetic testing has documented variability in overall levels of awareness and by geographic location, age, income, and education [11, 14, 15]. Limitations of prior research stem from the lack of national samples [11, 14] and failure to more fully explore demographic, behavioral, and geographic covariates of awareness to facilitate a more complete understanding of the implications of DTC marketing activities.

The Health Information National Trends Survey sought to fill this research gap by including a question about awareness of DTC genetic test marketing on a nationally representative survey platform [16]. Prior analysis of the 2008 Health Information National Trends Survey (HINTS) data explored associations of awareness with numeracy and identified racial and ethnic differences [16]. Our research provides a more detailed analysis of the 2008 data and includes analysis of 2011 HINTS data to explore trends in awareness over time.

Specifically, our research assesses changes in awareness of DTC genetic testing in the US population and explores factors associated with awareness including sociodemographic characteristics, cancer history, health care access, Internet use, and geographic differences. We focus on these factors for a variety of reasons. First, many of the currently available DTC genetic testing companies offer cancer risk testing as a major component of their service; in fact, the first major DTC multimedia advertising campaign for a genetic test was for breast cancer [17]. We included prior cancer diagnosis and family history of cancer in our analyses to explore whether individuals with particular interest in cancer are more aware of these services and thus may be part of the potential market for these services. Second, while proponents of DTC genetic testing have suggested that this mode of testing might facilitate greater access to genetic services in underserved areas [18], this has not yet been empirically examined. If awareness of these services is confined to urban areas and individuals who already have more health care access, then DTC genetic testing could exacerbate already-existing disparities in health care resources. Third, the majority of DTC genetic testing marketing efforts occur on-line. Thus, we were interested in exploring whether use of the Internet was associated with awareness of DTC genetic testing. Finally, given the unequal distribution of high speed Internet access in the USA with particular disparities in rural America, and the urban-focused efforts of traditional media marketing campaigns, we sought to discern whether there were differences in awareness of DTC genetic testing by population density [19].

2. Materials and Methods

2.1. Data Source. We analyzed data from two iterations of the Health Information National Trends Survey (HINTS 2008 and HINTS 2011). HINTS is a nationally representative survey of the US adult population that tracks trends in cancer-related attitudes, knowledge, and behavior [20]. HINTS 2008 data were collected using a mixed mode, dual-frame design ($n = 7,674$) including both a list-assisted Random Digit Dial (RDD) Computer-Assisted Interview ($n = 4,092$) and comprehensive national listing of addresses available from the United States Postal Service for a mailed questionnaire ($n = 3,582$). HINTS 2011 data were collected via a comprehensive national listing of addresses available from the United States Postal Service for a mailed questionnaire ($n = 3959$). Further details on survey design and sampling strategies for both surveys have been published elsewhere [21, 22].

2.2. Data Collection and Response Rates. For HINTS 2008, the RDD data collection effort was conducted from January 7 to April 27, 2008, and the mail survey was conducted from January 15 to April 27, 2008. For the RDD arm, one adult from each sampled household was selected for an interview. The mail arm of HINTS 2008 included a stratified sample selected from a list of addresses, with an oversampling of minorities. The mail sample was a stratified cluster sample, in which the household was the cluster, therefore, for each sampled address all adults in the household were asked to complete a questionnaire. The response rate for the RDD household screener was 42.4%, and the response rate for extended interview was 57.2%, resulting in an overall RDD response rate of 24.2%. The household response rate for the mail survey was 40%, and the within-household rate was 77%, resulting in an overall response rate of 31%.

Data collection for HINTS 2011 was initiated in October 2011 and concluded in February of 2012. The sample design involved two stages wherein a stratified sample of addresses was selected from a file of residential addresses, and respondents were selected within each sampled household. Two methods of respondent selection were used: the "next birthday" method requested that the adult in the household with the next birthday complete the questionnaire and the "all adult" method requested that each adult in the household complete a questionnaire [22]. Household response rates were calculated separately for each respondent selection method [23]. For the next birthday method of respondent selection, the household response rate was 37.9% and the household response rate for the all adult method was 35.3%. For the all adult method the household response rate was 84.6%. The final response rate for HINTS 2011, determined by combining response rates across respondent selection method in proportion to the allocated sample, was 36.7%.

2.3. Measures

Awareness of Direct-to-Consumer Genetic Tests. The following question assessed awareness of DTC genetic tests in both 2008 and 2011: *Genetic tests that analyze your DNA, diet, and lifestyle for potential health risks are currently being marketed by companies directly to consumers. Have you heard or read about these genetic tests?*

Sociodemographic Variables. Sociodemographic variables included gender, age (18–34, 35–49, 50–64, 65–74, and 75+ years), education (less than high school, high school graduate, some college, and college graduate), annual household income (less than $35K, $35K to less than $75K, and $75K or more), and race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and "other").

Health Care Access. Two indicators of health care access were included in our analyses: health insurance status and usual source of health care. Health insurance status was assessed with the following item in 2008*: Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicare? (yes/no)*. In 2011, this item was revised as follows: *Do you have any of the following health insurance or health coverage plans: Insurance through a current or former employer or union (of you or another family member); Insurance purchased directly from an insurance company (by you or another family member); Medicare; Medicaid, Medical Assistance, or any kind of government assistance plan for those with low incomes or disability; TRICARE or other military health care; VA (including those who have ever used or enrolled for VA health care);* or *Indian Health Service.* Responses to the 2011 item were recoded as *yes/no* to be comparable with 2008 wherein those who indicated having at least one source of health insurance were coded as yes.

In 2008 and 2011, regular source of health care was assessed with the following item: *not including psychiatrists and other mental health professionals, is there a particular doctor, nurse, or other health professional that you see most often?* Responses to both items were coded as yes/no.

Cancer History. Respondents were asked about their personal history of cancer in both 2008 and 2011 with the following question: *Have you ever been diagnosed as having cancer?* Respondents to both surveys were also asked*: Have any of your family members ever had cancer?* Responses were coded as yes/no.

Internet Use. The following item assessed use of the Internet: *Do you ever go online to access the Internet or World Wide Web, or to send and receive e-mail*? Responses were coded as yes/no.

Population Density. For HINTS 2008 and 2011, county-level rural-urban continuum codes are determined from the US Department of Agriculture Economic Research Service for each respondent according to their geographic location. For our analyses, the original continuum represented by 9 rural-urban codes was recoded to create a two-level variable wherein counties in metro areas were coded as urban and those in non-metro areas were coded as rural.

2.4. Data Analysis. We used SUDAAN version 9.0.1 to estimate standard errors of point estimates for the complex survey data [24]. All data were weighted according to population estimates in the American Community Survey to provide representative estimates of the adult US population. Jackknife replicate weights were computed to get accurate variance estimates. To address the issue of nonindependence of responses from members of the same household, all respondents from the same household were assigned to the same replicate weights which accounts for clustering within the primary household sampling unit [25]. A cross-tabulation with chi square of survey mode of administration for the 2008 data (RDD/mail) with the primary outcome variable, awareness of DTC genetic tests (yes/no), revealed that there were no mode of survey administration effects on the estimates for the RDD and mail survey; therefore, data from the RDD and mail survey were combined for our analyses.

Cross-tabulations and chi-square tests of association were conducted for awareness of DTC genetic tests by sociodemographic, health care access, Internet use, and geographic characteristics for each survey year. We created a combined dataset integrating data and relevant variables including sampling variables and weights from 2008 and 2011 resulting in a combined sample size of $n = 11,633$. We then conducted a multivariable logistic regression analysis to examine independent associations with awareness including survey year, sociodemographic, health care access, Internet use, and population density using a forced entry method of variable selection. Missing data were treated listwise in the multivariable model and indicator variables were created for missing values for income ($n = 1760$ missing) and family history of cancer ($n = 1094$ missing) to reduce the impact of missing values for these variables on the model.

3. Results

In 2008, 29.3% of the population was aware of DTC genetic tests. The percentage of the population aware of DTC genetic tests increased significantly to 36.9% in 2011 (Table 1). Cross-tabulation of the respondents' sociodemographic characteristics with awareness of DTC genetic tests in each survey year revealed several significant bivariable correlations (Table 1).

To assess whether the observed increase in awareness held while controlling for sociodemographic characteristics, health status, Internet use, and population density we conducted a multivariable analysis on the combined 2008 and 2011 data (Table 2). Survey year remained significantly associated with awareness with the additional variables included in the model; awareness in 2011 was significantly higher (OR = 1.39) than in 2008. The odds of awareness of DTC genetic tests were significantly higher among those aged 50–64 (OR = 1.64), and 65–74 (OR = 1.60) compared to those aged 18–34. Awareness was also higher among college

Table 1: Awareness of direct-to-consumer genetic testing by respondent characteristics.

Respondent characteristic	Weighted[1] population % aware of DTC genetic tests	
	HINTS 2008	HINTS 2011
	$n = 7{,}674$	$n = 3{,}959$
Total ($\chi^2 = 32.64$; $P < 0.0001$)	**29.3**	**36.9**
Gender	($\chi^2 = 1.9$; $P = .18$)	($\chi^2 = 2.1$; $P = .15$)
Male	30.2	35.0
Female	28.3	39.1
Age	($\chi^2 = 13.3$; $P < .0001$)	($\chi^2 = 11.0$; $P < .0001$)
18–34	23.3	30.3
35–49	31.1	36.3
50–64	34.9	45.9
65–74	32.4	42.2
75+	24.1	30.3
Annual income	($\chi^2 = 32.7$; $P < .0001$)	($\chi^2 = 17.6$; $P < .0001$)
< $35K	25.7	29.0
$35K to < $75K	25.4	35.6
$75K or more	37.9	46.7
Race/ethnicity	($\chi^2 = 6.4$; $P < .01$)	($\chi^2 = 9.8$; $P < .0001$)
Non-Hispanic white	30.9	41.5
Non-Hispanic black	23.7	30.0
Hispanic/Latino	24.9	24.2
Non-Hispanic other	33.9	31.8
Education	($\chi^2 = 48.5$; $P < .0001$)	($\chi^2 = 21.5$; $P < .0001$)
Less than high school	22.9	21.0
High school	21.5	30.0
Some college	28.1	36.0
College graduate	42.9	48.2
Health insurance	($\chi^2 = 9.7$; $P < .01$)	($\chi^2 = 8.9$; $P < .005$)
Yes	30.5	40.6
No	24.2	32.8
Regular provider	($\chi^2 = 14.3$; $P < .001$)	($\chi^2 = 24.3$; $P < .0001$)
Yes	31.2	41.8
No	25.6	28.6
Prior cancer diagnosis	($\chi^2 = 8.5$; $P < .01$)	($\chi^2 = 23.6$; $P < .0001$)
Yes	34.0	47.4
No	29.0	35.9
Family history of cancer	($\chi^2 = 5.0$; $P < .05$)	($\chi^2 = 5.2$; $P < .05$)
Yes	31.0	40.5
No	26.4	34.6
Internet use	($\chi^2 = 23.0$; $P < .0001$)	($\chi^2 = 21.3$; $P < .0001$)
Yes	31.7	40.2
No	24.1	25.1
Rural-urban designation	($\chi^2 = 6.2$; $P < .05$)	($\chi^2 = 2.3$; $P = .13$)
Urban	30.2	37.6
Rural	25.0	33.5

[1] All data were weighted to be representative to the US population according to estimates from the American Community Survey.

graduates (OR = 2.02) compared to those with less education. Those with a regular source of health care (OR = 1.27) evidenced greater odds of awareness than those without. The odds of awareness of DTC genetic tests were significantly higher among persons with a prior cancer diagnosis (OR = 1.24) compared with those without. Those who used the Internet (OR = 1.27) had greater odds of awareness compared to those who did not use the Internet and those living in urban areas (OR = 1.25) had greater odds of awareness compared with those in rural areas.

Table 2: Independent correlates of awareness of direct-to-consumer (DTC) genetic testing ($n = 10,394$)[1].

	Odds ratio	95% confidence interval	P value
Survey year			
HINTS 2008	1.00	—	—
HINTS 2012	1.39	1.19–1.64	0.0001
Gender			
Female	1.00	—	—
Male	0.98	0.83–1.16	0.8507
Age			
18–34	1.00	—	—
35–49	1.26	0.99–1.60	0.0583
50–64	1.64	1.31–2.05	0.0000
65–74	1.60	1.18–2.18	0.0031
75+	1.14	0.81–1.60	0.4573
Race/ethnicity			
NH white	1.00	—	—
NH black	0.79	0.62–1.00	0.0499
Hispanic/Latino	0.82	0.62–1.09	0.1719
NH other	0.87	0.65–1.17	0.3628
Annual income			
Less than $35,000	1.00	—	—
$35,000 to < $75,000	0.90	0.73–1.13	0.3689
$75,000 or more	1.22	0.97–1.53	0.0896
Missing	1.39	1.02–1.91	0.0402
Education			
Less than HS	1.00	—	—
HS graduate	1.05	0.75–1.46	0.7765
Some college	1.31	1.00–1.72	0.0511
College graduate	2.02	1.49–2.75	0.0000
Health insurance			
Yes	1.00	—	—
No	1.10	0.90–1.35	0.3516
Regular provider			
No	1.00	—	—
Yes	1.27	1.04–1.54	0.0178
Prior cancer diagnosis			
No	1.00	—	—
Yes	1.24	1.07–1.44	0.0047
Family history of cancer			
No	1.00	—	—
Yes	1.13	0.98–1.32	0.0951
Missing[2]	0.77	0.53–1.12	0.1638
Internet use			
No	1.00	—	—
Yes	1.27	0.97–1.67	0.0823
Population density			
Rural	1.00	—	—
Urban	1.25	1.05 –1.49	0.0144

[1] Missing values in model are listwise; if any case is missing a value on any of the variables they are dropped from the analyses.
[2] This category includes (1) "Has no family" ($n = 15$), (2) "Refused," (3) "Do not know," and (4) missing for 2008 data; For the 2012 data, this category includes (1) "Missing data (Not Ascertained)," (2) "Multiple responses selected in error," and (3) "Not sure."

4. Discussion

Our nationally representative results suggest that while general levels of awareness of DTC genetic tests have increased in the past 4 years, increased awareness is not equally distributed throughout the population. Independent of survey year, the odds of awareness of DTC genetic tests were significantly higher for the following: those aged 50–74, those with greater education, those with a regular source of care, those with a prior cancer diagnosis, those who use the Internet, and those living in urban areas. Estimates of awareness from 2008 are generally consistent with prior research [11, 14, 15], and the differences in awareness of DTC genetic testing observed by age and education were similar to those reported in previous research [11, 16]. Although we document a persistence of these differences across two time periods, thus advancing earlier work, our results also expand on previous research by documenting greater awareness of DTC genetic tests for those individuals with a regular source of care and those with a prior cancer diagnosis. Finally, use of the Internet and residence in population-dense regions of the country were associated with greater awareness of DTC genetic tests paralleling options for high speed Internet connections throughout the county [19].

Accurate understanding of the population prevalence of public interest in DTC testing is important to inform ongoing discussions of its public health and policy implications. Our results reveal that certain groups of the public have been reached by DTC marketing efforts to a greater extent than others; namely, higher SES populations with more Internet savvy. Thus, to the extent that DTC genetic testing has value for public health (a contention that remains under evaluation [6, 26]), the consumers likely to reap the benefits are those already advantaged in health care. Our study also reveals the possibility that individuals with cancer risk may be particularly attracted to DTC modes of testing, supporting the importance of empirical research that focuses on the attitudes, beliefs, and responses to testing among subgroups defined by disease risk [27]. Of course, awareness of testing is likely to far exceed use of services; previous research has suggested that while 22% of people were aware of services in 2008, less than 1% had used them [15]. More research is needed to understand consumers' rationales for their decisions to actually pursue DTC genetic testing. Moreover, an in-depth analysis of the public health benefits and risks and policy implications of DTC genetic services will depend on the results of research, using both qualitative

and quantitative research methods, on DTC service users. A wealth of recent initiatives to explore the impact of personal genomic risk information on individual users' attitudes, beliefs, mental health, health behaviors, and health services have already added, and will continue to add, to the evidence base [3, 12, 13, 26, 28].

A few limitations are worth noting. The HINTS program provides data from rigorously developed samples based on cross-sectional surveys. As such, it is not possible to make inferences about causality in observed relationships. Another limitation of the HINTS data stems from the relatively low response rates. With the development of Caller ID and the progression toward cell phone only households, response rates for RDD surveys have fallen over the past decade [29, 30]. However, recent methodological research suggests that the potential for bias resulting from declining RDD response rates may not be as significant for health surveys as previously assumed [30–32]. Considerable effort has also been made in the HINTS program to protect against biases introduced through modality, coverage, and sampling through use of dual frame administration in 2007-2008 [33]. The use of the mailed survey in 2008 and 2011 provides access to cell phone only households. Another limitation stems from missing data; in particular, in the multivariable model, missing data were treated listwise so cases with missing values on any of the variables included in the model were dropped from the model leading to a large number of missing values which may limit the generalizability of the results. However, to reduce the number of cases dropped from the model we created indicator variables to represent missing values for income and family history. Finally, it is important to note that our one-item measure of awareness of DTC genetic tests does not capture the complexity and multifaceted nature of the many types of tests available, and thus, is a relatively blunt measure of awareness. However, national survey tools are often constrained to measuring constructs of interest with only one or two items given the overall limits placed on survey length and respondent burden.

5. Conclusions

Controversy and uncertainty around the risks and benefits of DTC genetic testing, coupled with limited regulatory oversight [1, 34, 35], underscore the importance of tracking public awareness of DTC genetic testing as a proxy for current and future demand for these services. The nationally representative data described herein reveals growing awareness of DTC genetic testing that is unequally distributed in the population. The HINTS program will continue to monitor awareness of DTC genetic testing to track changes over time.

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Research Article

Genetic Influences on Physiological and Subjective Responses to an Aerobic Exercise Session among Sedentary Adults

Hollis C. Karoly,[1] Courtney J. Stevens,[1] Renee E. Magnan,[2] Nicole Harlaar,[1] Kent E. Hutchison,[1] and Angela D. Bryan[1]

[1] *Department of Psychology and Neuroscience, University of Colorado at Boulder, 345 UCB, Boulder, CO 80309-0345, USA*
[2] *Department of Psychology, University of New Mexico, MSC03 2220, Albuquerque, NM 87131, USA*

Correspondence should be addressed to Hollis C. Karoly, hollis.karoly@colorado.edu

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Objective. To determine whether genetic variants suggested by the literature to be associated with physiology and fitness phenotypes predicted differential physiological and subjective responses to a bout of aerobic exercise among inactive but otherwise healthy adults. *Method*. Participants completed a 30-minute submaximal aerobic exercise session. Measures of physiological and subjective responding were taken before, during, and after exercise. 14 single nucleotide polymorphisms (SNPs) that have been previously associated with various exercise phenotypes were tested for associations with physiological and subjective response to exercise phenotypes. *Results*. We found that two SNPs in the *FTO* gene (rs8044769 and rs3751812) were related to positive affect change during exercise. Two SNPs in the *CREB1* gene (rs2253206 and 2360969) were related to change in temperature during exercise and with maximal oxygen capacity (VO_2 max). The *SLIT2* SNP rs1379659 and the *FAM5C* SNP rs1935881 were associated with norepinephrine change during exercise. Finally, the *OPRM1* SNP rs1799971 was related to changes in norepinephrine, lactate, and rate of perceived exertion (RPE) during exercise. *Conclusion*. Genetic factors influence both physiological and subjective responses to exercise. A better understanding of genetic factors underlying physiological and subjective responses to aerobic exercise has implications for development and potential tailoring of exercise interventions.

1. Introduction

In the United States, insufficient participation in leisure time physical activity constitutes a major threat to public health. Recent estimates suggest that 25% of Americans do not engage in any physical activity at all [1]. Even those engaging in physical activity are usually not doing so at recommended levels. In order to promote and maintain health, the American College of Sports Medicine (ACSM) recommends a minimum of 30 minutes of moderate intensity aerobic physical activity five days a week or a minimum of 20 minutes of vigorous intensity aerobic physical activity three days a week [2]. Despite these widely disseminated guidelines, the Centers for Disease Control (CDC) report that Americans have made "no substantial progress towards achieving recommended levels of physical activity" with the proportion of 18–29 year olds meeting guidelines hovering around 35% and the proportion of adults 65 and older meeting guidelines at about 20% [1].

These numbers are troubling, as aerobic exercise has been convincingly linked to the prevention of myriad negative health outcomes, including several forms of cancer. Numerous studies conducted over the past two decades have explored the association between physical activity participation and cancer prevention, consistently implicating strong or probable evidence for reduced risk of colon, breast, and endometrial cancers when physical activity recommendations are followed [3–6]. Likely mechanisms through which physical activity is believed to have an influence on cancer prevention include reduction in adiposity and changes to

levels of circulating metabolic hormones and growth factors (e.g., estrogen, testosterone, and insulin-like growth factors) [7–9] as well as influences on DNA methylation [10, 11]. In respect to prostate cancer, because physical activity activates gut motility, gastrointestinal transit time for food wastes is lessened and thus, exposure to carcinogens is attenuated [7]. There is also research to suggest that immune function changes may mediate the relationship between physical activity and cancer development [9].

The promising body of literature regarding the relationship between physical activity and cancer has led the National Cancer Institute (NCI) to regard behavioral primary prevention of cancer (e.g., physical activity) as a top priority [12]. Unfortunately, interventions designed to change behavior are typically met with only modest success, even when grounded in empirically supported theory [13], and behavioral adherence is reported to be a principal challenge faced by exercise promotion programs [14]. Indeed, only 50% of individuals who adopt an exercise program stay with it for more than six months [14, 15]. Researchers devoted to the goal of improved physical activity participation have suggested that one likely determinant of physical activity behavior is the way in which individuals subjectively experience exercise [16].

In previous work, we organized genetic, physiological, subjective, and motivational factors that may contribute to the initiation and maintenance of physical activity into a conceptual transdisciplinary framework [16, 17]. This framework has received support among both active [16] and inactive [17] samples, and provides the basis for the selection of phenotypes in the current study. Briefly, we proposed that genetic factors influence how an individual physiologically (e.g., body-temperature regulation) and subjectively (e.g., affective response, perceived exertion) responds to the experience of exercise. Physiological response influences how one subjectively responds to the experience of exercise (e.g., increased lactate during exercise may increase perceived exertion) and these subjective responses influence motivation to exercise (e.g., exercise self-efficacy, exercise intentions). Exercise motivation then influences the likelihood of engaging in exercise. Moreover, exercise behavior itself influences both how a person physiologically responds to the experience of exercise and gene expression [18], thereby recapitulating the framework. Importantly, this framework is meant to be dynamic such that the factors selected to represent physiological response, subjective response, and/or motivation can vary depending on the goals of each individual research study.

The relationship between physiological changes induced by aerobic exercise (e.g., regulation of body temperature, heart rate, or blood pressure during exercise) and subjective responses to aerobic exercise (e.g., changes in affect during or immediately after exercise, ratings of perceived exertion or pain during an exercise bout) is one that has a clear influence on individual differences in exercise behavior. Bryan and colleagues [16] found that physiological factors such as heart rate were related to mood response to exercise, and that mood response was a significant correlate of both motivation to exercise in the future and of current exercise behavior. Additionally, subjective experiences during exercise may be influenced by interpretations of exercise-induced physiological responses. For instance, increases in lactate levels during aerobic exercise may be perceived as painful to varying degrees across individuals, and this perceived pain will in turn influence subjective exercise experiences and potentially impact motivation to engage in exercise behavior in the future. Understanding potential influences on subjective response to exercise is especially important, given that affective responses to acute exercise have been found to predict long-term exercise behavior [19, 20].

Although the heritability of exercise participation in adults has been shown in twin studies to be approximately 50% (with peak heritability of 85%, occurring at age 19-20) [21, 22], there is a surprising lack of research regarding the role played by genetic factors for determining physiological and affective responses to exercise. These responses may serve as promising intermediate phenotypes for the linkage of genes to broader exercise participation phenotypes [23]. Also important is the notion of a "gene by exercise interaction," explained by de Geus and de Moor [21] as the genetic variance causing differential responses to exercise training, given that the effects of exercise on health and fitness gains appear not to be uniform across individuals [24, 25]. One type of gene-by-exercise interaction that is relevant to the present study is the role of exercise in reducing the phenotypic effects of some detrimental genetic variants. For example, Phares et al., [26] showed that sedentary individuals who possess two particular polymorphisms of the *ADR* gene have unfavorable body composition. However, these individuals experience greater loss in percent body fat after 24 weeks of aerobic training in comparison with all other genotypes. It follows that weight loss interventions for individuals with this particular genotype would likely be successful if they focused on aerobic training. Thus, identifying particular genetic markers that are related to exercise behavior and physiological and affective responses to exercise may have clear implications for matching individuals to tailored exercise intervention programs.

The goal of the current study is to determine whether genotypes predicted subjective physiological and affective responses to a 30-minute bout of aerobic exercise among sedentary individuals. Based on the literature and on our prior analysis of the relationships among a range of exercise response phenotypes (see [17] for analysis and detailed information on the rationale for selection of phenotypes), the variables from the physiological responses to exercise domain included in our analysis were temperature, heart rate, systolic blood pressure, lactate, and norepinephrine, all measured as change scores from immediately prior to a bout of exercise to 30-minutes into the bout (just before the end of the bout). Genetic associations with VO_2 max were also examined, as cardiovascular fitness is highly heritable [27–30], and evidence exists for a strong genetic influence on athletic performance [31]. Additionally, genetically influenced cardiovascular fitness traits play a role in determining individual experience of exercise intensity and perception of exertion during exercise [32]. The variables selected from the subjective experience of exercise domain were affect (i.e., positive affect and affective valence), perceived pain, and rate

of perceived exertion (RPE) [17], which were also change scores measured from prior to the bout to just before the end of the bout.

We chose the specific genetic factors for our analyses a priori based on evidence from the literature that they were linked to processes related to physiological and subjective responses during physical activity, general health and fitness traits, or because of evidence that they moderate responses to exercise interventions. A single nucleotide polymorphism (SNP) in the fat mass and obesity-associated protein gene (*FTO;* rs9930506) has been associated with obesity traits such as increased BMI and weight [33] and susceptibility to obesity [34]. Additionally, physical activity may slow down weight gain associated with the *FTO* risk-allele [35]. In addition, the μ-opioid receptor gene (*OPRM1*) may be associated with pain sensitivity such that individuals possessing the rare G allele have an increased pressure pain threshold [36]. Interestingly, this study also found gender differences in pain threshold among individuals with the G allele when heat pain was tested, such that women with this allele have lowered pain thresholds, and men exhibit higher pain thresholds. SNPs located within in the *SLIT2* gene(rs1379659), *FAM5C* gene (rs1935881), *KCNB2* gene (rs10505543), and rs10498091 (an SNP associated with left ventricle mass) have all been found to be associated with echocardiography traits (e.g., left ventricle diastolic dimension, diameter, and systolic dimension) in a genome-wide association study [37]. Another genome-wide analysis implicated *CREB1* in the prediction of submaximal exercise heart rate in response to exercise training [38, 39]. Thus, each of these SNPs was investigated in the current study in order to determine potential relationships with phenotypes related to physiological and affective response to an acute bout of aerobic exercise.

2. Methods

2.1. Participants. Participants included in the present analysis were a subset of 238 individuals from a larger intervention study (COSTRIDE) [17, 40] in which participants were randomly assigned to the STRIDE exercise intervention (COSTRIDE) or a health-and-wellness contact control condition (HW). Participants were men and women (ages 18–45) who reported less than 90 minutes on average of at least moderate-intensity physical activity per week for the past three months. Individuals were excluded if they smoked cigarettes, were on a restricted diet, were taking psychotropic medications, were receiving treatment for any psychiatric disorder, were diabetic, had a history of cardiovascular or respiratory disease, had the flu or illness within the last month, or were pregnant (if female). All participants were required to be willing to be randomized to an intervention condition, to give informed consent, to be able to engage in moderate-intensity physical activity, to have a body mass index (BMI) between 18 and 37.5, and to have a regular menstrual cycle (if female). All participants were recruited from the Denver-metro area and the University of Colorado Boulder community [25]. The data reported herein are from assessments conducted prior to randomization, and the analysis and questions addressed are unique to this investigation.

As described in detail below, we used the Illumina Human 1M DuoV3 DNA Analysis BeadChip to genotype the DNA samples. The bead chips accommodate 4 samples each, and we ran a total of 50 bead chips. Thus, this experiment allowed for the genotyping of 200 individuals total. Due to limitations in funding, we were unable to genotype the remaining 38 individuals in the sample. Thus, individuals with the most complete baseline data (baseline DNA sample, self-report questionnaire assessments, VO_2 max fitness assessment, and submaximal exercise session) were selected to be genotyped out of the full sample.

Statistical tests revealed no significant differences on demographic variables between participants who were included in genotyping procedures and those who were not included in genotyping procedures (details available from the first author). This reduced sample (N = 200) was comprised primarily of females (n = 160) and most participants identified as white (n = 137), followed by Hispanic/Latino (n = 22), Asian American (n = 22), African American (n = 9), Native American (n = 5), and mixed ethnicity (n = 5), The average age of participants at baseline was 28.68 (SD= 7.86) years old and mean body mass index (BMI; weight in kg/height in m^2) was 25.18 (SD = 4.72). On average participants reported an average of 28.14 minutes of voluntary physical activity in the past week (SD= 50.95), and reached an average VO_2 max peak of 34.06 mL/kg/min (SD= 8.11). Additional demographic characteristics are reported in Table 1.

2.2. Procedure. Prior to randomization to intervention condition and after giving informed consent, participants completed three sessions: (1) an orientation (baseline) session in which self-report questionnaire assessments were completed, (2) a VO_2 max cardiovascular fitness assessment, and (3) a submaximal exercise session. Prior to exercise sessions, each participant was instructed to eat a meal comprised of both carbohydrates and protein and to consume at least 300 calories two hours before coming into the lab (e.g., If a participant is scheduled to come into the lab at 12:00 p.m. a researcher instructed him/her to eat the 300 calorie meal at 10:00 a.m. and no later). Participants were also instructed to drink at least 17 oz. of water two hours prior to coming into the lab. Participants were instructed not to exercise on their own prior to the laboratory session, and not to consume alcohol during the 24 hours prior to testing. Further details regarding recruitment, selection of measures, and study procedures are available elsewhere [17]. This research was approved by all relevant institutional review boards.

2.2.1. Cardiorespiratory Fitness Test (VO_2 Max). Consistent with established procedures [41], maximal oxygen capacity (VO_2 max) was assessed during a Balke protocol (a graded, incremental exercise test) on a motorized treadmill [42]. VO_2 max was assessed with online computer-assisted open-circuit spirometry using the Medgraphics Cardi02/CP system. Prior

Table 1: Sample demographics.

Characteristic	Frequencies	*M*
N	200	
Gender		
Female	160	
Male	40	
Age		28.68 (SD = 7.86)
18–25	78	
26–35	74	
36–45	48	
BMI		25.18 (SD = 4.72)
Underweight (≤18.49)	3	
Normal weight (18.50–24.99)	101	
Overweight (25.00–29.99)	57	
Obese (30.00–34.99)	29	
Extreme obese (≥35.00)	7	
Ethnicity		
White	137	
African American	9	
Asian	22	
Hispanic/Latino	22	
Native American	5	
Mixed ethnicity	5	
Other	0	
Number of years of education		15.81 (SD = 2.64)
≤12	22	
13–16	117	
17–20	53	
21–24	5	
25-26	3	
Average annual household income		
$0–9,999	14	
$10–29,999	39	
$30,000–49,999	37	
$50,000–69,999	40	
$70,000–89,999	31	
$90,000–109,999	20	
≥ $110,000	14	

Note: SD: standard deviation. BMI: body mass index. BMI is calculated as weight in kg/height in m^2.

to the fitness test, saliva samples (5 mL) were collected for DNA extraction and measurements of height and weight were taken for calculation of BMI.

2.2.2. Submaximal Exercise Session. Approximately one week after the fitness test, participants completed a standardized, short 30-minute bout of physical activity on the treadmill at 65% of their previously established VO_2 max, calculated during the fitness test (VO_2 max test session). Prior to beginning activity, an intravenous catheter was inserted by a nurse to collect blood samples during the bout. Intensity was maintained by measuring oxygen uptake and expired CO_2 for two to three minutes at the beginning of exercise and at 10 and 20 minutes during exercise.

2.2.3. Physiological Phenotypes. Lactate concentration and *catecholamine levels* (epinephrine and norepinephrine) were collected via blood samples immediately before activity began (11.5 mL), and 10 (5.5 mL) and 30 (11.5 mL) minutes into activity. *Tympanic temperature* was measured by taking an average of 2-3 temperature readings at each measurement. Readings of temperature, *blood pressure, and heart rate* were taken before activity, at 10 minutes, 20 minutes, and 30 minutes (directly before completion) during activity.

2.2.4. Subjective Phenotypes. Subjective experiences during exercise were assessed at six points during the submaximal session: five minutes prior to activity, immediately before activity began, and 10, 20, and 30 minutes into activity (directly before completion of the session). The present study focuses only on change scores created from subtracting the values obtained immediately before the exercise bout began from the values obtained 30 minutes into the bout. For the time points that occurred 10, 20, and 30 minutes into the exercise bout, participants were assessed while they were exercising—the bout was not interrupted to make these assessments. While participants continued their session on the treadmill, a research assistant held up cards with the questionnaire items displayed on them. Participants indicated the number that they felt reflected their current subjective states, and their responses were manually recorded. Physiological measures were obtained at these time points using the IV catheter that was inserted prior to the bout. *Positive affect* was assessed using 3 items from the 12-item physical activity affect scale (PAAS) [43]. The positive affect subscale is computed by taking the average of the three items. Participants rated their current state for each item using a 5-point scale (0 = do not feel to 4 = feel very strongly). The adjectives assessed by the 3-item positive affect subscale were enthusiastic, energetic, and upbeat (α = .81). *Affective valence during exercise* was assessed using the 11-point single-item feeling scale (FS) [44], which ranges from −5 = very bad to +5 = very good. *Perceived exertion* was assessed using the 15-point single-item *rating of perceived exertion* (RPE) [45] that ranges from 6 to 20 (6 = no exertion at all, 20 = maximal exertion). *Perceived pain* was assessed using a single-item 12-point borg category ratio-10 scale (CR10) (0 = no pain at all, 10 = extremely intense pain) [45].

2.3. DNA Processing and SNP Selection. Genomic DNA was extracted from saliva samples of 200 participants. Samples were genotyped on the Illumina Infinitum Assay Platform using the Human 1M DuoV3 DNA Analysis BeadChip (Illumina, Inc., San Diego, CA, USA) following the manufacturer's protocol at the University of Colorado, Boulder. In this assay, the DNA undergoes whole genome amplification, followed by fragmentation and ethanol precipitation. The DNA is then resuspended in hybridization buffer and applied to the bead chip array for an overnight incubation. The amplified and fragmented DNA samples

anneal to locus-specific 50-mers (covalently linked to one of over 1,000,000 bead types) during the hybridization step. Following hybridization, the arrays are washed to eliminate unhybridized and nonspecifically hybridized DNA. One bead type corresponds to each allele per SNP locus. The samples then undergo single-base extension and staining, followed by more washing. The arrays are allowed to dry, and then scanned using the Illumina iScan system. Genotype calls were made using Illumina's GenomeStudio software in conjunction with the Genome Studio genotyping module. We removed SNPs with a genotype call rate <98%. Additionally, we excluded SNPs with a minor allele frequency (MAF) of <10% and SNPs that showed significant deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$). Following these quality control checks, a total of 842,777 SNPs remained available for analysis.

Although we used a genome-wide approach to genotyping, we only tested a total of 14 SNPs which were selected for analysis in this study based upon their potential association with aerobic exercise response phenotypes suggested by prior studies (see Table 2 for Hardy-Weinberg P values and minor allele frequencies for each SNP tested). Our search was conducted primarily using PubMed, and was focused on SNPs that were directly associated with specific phenotypes of interest and to traits that may be associated with those phenotypes. Analyses were run using the SNP and Variation Suite for Genetic Analysis (SVS) (version 7.5.6, Golden Helix Inc., Bozeman, MT). The 14 SNPs selected for inclusion based on our search were tested for associations with the phenotypes using a correlational trend test assuming additive effects of allele dosages for each SNP (i.e., homozygous for the minor allele = 0; heterozygous = 1; homozygous for the major allele = 2).

3. Results

These analyses focused on correlations between particular SNPs suggested by the relevant literature and exercise response phenotypes drawn from our previous work and the existant exercise literature. Due to the fact that both exercise phenotypes and candidate SNPs were selected a priori based on the literature as well as our transdisciplinary framework, critical alpha for all tests was maintained at the .05 level for all analyses. Additionally, given that the aim of this study was to examine changes in physiological and subjective responses to exercise over the course of the 30-minute exercise bout, it was not necessary to compare subjects cross-sectionally at the baseline or 30-minute time points. Rather, all phenotype values were determined using a change score created by subtracting each subject's baseline values from the values obtained by that subject 30 minutes after the exercise bout began.

3.1. Genotype Differences by Race. In order to determine whether allele frequencies for all SNPs examined in this study were significantly different across racial/ethnic groups, χ^2 tests were performed on all SNPs based on racial categories. χ^2 test statistics and corresponding P values are included in Table 3. Additionally, major and minor alleles, as well as minor allele frequencies (MAFs) for Caucasians, African Americans, Asians, and Hispanic/Latino participants are reported in Table 3. Significant differences in genotype across racial/ethnic groups were found for three SNPs, rs1935881 $\chi^2(10, 200) = 19.25$, $P = .037$, rs1799971 $\chi^2(10, 200) = 38.13$, $P < .001$, and rs8044769 $\chi^2(10, 200) = 21.54$, $P = .018$. For rs1935881, the MAF is lower among Asians. For rs1799971, an MAF of 0 was found in African Americans. For rs8044769, the MAF is also lowest in African Americans. Results of associations between SNPs and exercise response phenotypes presented below are uncorrected (no PCA correction applied).

3.2. Correlations between Phenotypes. A total of 10 different phenotypes were examined for association with genetic variants in this study. Given that many of these phenotypes may have common underlying physiological bases, we tested for associations between these phenotypes. In the following results, all phenotypes tested and reported (except for VO_2 max) refer to a change score created by subtracting preexercise values from the values obtained 30 minutes into the exercise bout. Results of these analyses are reported in Table 4. VO_2 max was significantly correlated with change in lactate ($r = .177$, $< .05$), heart-rate ($r = .434$, $P < .01$), systolic blood pressure ($r = .193$, $P < .01$), and rate of perceived exertion ($r = .157$, $P < .05$) from baseline to 30 minutes into the exercise bout. Lactate change was correlated with temperature change ($r = .214$, $P < .01$), heart rate change ($r = .429$, $P < .01$), systolic blood pressure change ($r = .208$, $P < .01$), change in affective valence (as measured by the feeling scale) ($r = -.173$, $P < .05$), and pain change ($r = .215$, $P < .05$). Norepinephrine change was significantly correlated with positive affect change ($r = .174$, $P < .05$) and pain change ($r = -.165$, $P < .05$). Temperature change was significantly correlated with heart-rate change ($r = .172$, $P < .05$) and affective valence change ($r = .149$, $P < .05$). Heart rate change was significantly correlated with systolic blood pressure change ($r = .185$, $P < .05$) and rate of perceived exertion change ($r = .231$, $P < .05$). Rate of perceived exertion change was significantly correlated with affective valence change ($r = -.163$, $P < .05$) and pain change ($r = .316$, $P < .01$). Finally, positive affect change was significantly correlated with affective valence ($r = .455$, $P < .05$).

3.3. SNP Associations with Exercise-Response Phenotypes. Correlations between genotype and exercise-response phenotypes were calculated. Significant associations emerged for SNPs in five different genes. The *CREB1* SNPs rs2360969 and rs2253206 were associated with temperature change during exercise (rs2360969, $r = .17$, $P = .02$; rs2253206, $r = .17$, $P = .02$) indicating that for rs2360969, individuals with the T allele had greater changes in temperature over the course of the exercise, and for rs2253206, individuals with the A allele had greater changes in temperature during exercise. These same SNPs were also significantly associated with VO_2 max (rs2253206, $r = -.17$, $P = .01$; rs2360969, $r = -.14$ $P = .049$),

Table 2: Summary of all SNPs tested for associations with exercise-induced physiological or subjective response-change phenotypes in the STRIDE sample.

SNP	Chromosome	Position	Hardy-Weinberg equilibrium *P*	Minor allele frequency	Minor allele	Nearest gene locus
rs1935881	1	188333009	0.346	0.250	G	*FAM5C*
rs2360969	2	208081241	0.706	0.373	T	*CREB1*
rs2253206	2	208100223	0.400	0.453	A	*CREB1*
rs10498091	2	221607688	0.154	0.135	A	*intergenic*
rs1379659	4	20229781	0.068	0.165	G	*SLIT2*
rs1799971	6	154402490	0.529	0.178	G	*OPRM1*
rs8050136	16	52373776	0.277	0.350	A	*FTO*
rs3751812	16	52375961	0.119	0.333	T	*FTO*
rs11075989	16	52377378	0.172	0.358	T	*FTO*
rs7202116	16	52379116	0.172	0.358	G	*FTO*
rs7201850	16	52379363	0.228	0.371	T	*FTO*
rs9941349	16	52382989	0.104	0.345	T	*FTO*
rs7190492	16	52386253	0.768	0.400	A	*FTO*
rs8044769	16	52396636	0.159	0.490	T	*FTO*

Table 3: Summary of minor allele frequency (MAF) of each SNP tested separately for each racial/ethnic group.

SNP	Minor allele	Major allele	Caucasian MAF	African American MAF	Hispanic/Latino MAF	Asian MAF	χ^2 (10,200)	*P* value
rs1935881	G	A	0.288	0.222	0.159	0.068	19.25	**.03***
rs2360969	T	C	0.401	0.111	0.432	0.227	18.22	.051
rs2253206	A	G	0.438	0.444	0.477	0.386	10.56	.393
rs10498091	A	G	0.157	0.111	0.068	0.045	10.6	.389
rs1379659	G	A	0.197	0.000	0.114	0.136	10.05	.436
rs1799971	G	A	0.153	0.000	0.136	0.432	38.13	**<.001***
rs8050136	A	C	0.354	0.500	0.318	0.273	11.37	.329
rs3751812	T	G	0.354	0.167	0.318	0.273	7.22	.704
rs11075989	T	C	0.354	0.444	0.364	0.273	9.342	.5
rs7202116	G	A	0.354	0.444	0.364	0.273	9.342	.5
rs7201850	T	C	0.358	0.444	0.386	0.318	12.05	.676
rs9941349	T	C	0.358	0.167	0.341	0.318	10.27	.418
rs7190492	A	G	0.431	0.222	0.455	0.205	15.02	.131
rs8044769	T	C	0.467	0.167	0.432	0.273	21.54	**.018***

The * indicates *P* values that are less than .05

Table 4: Relationships between subjective response phenotypes ($N = 200$).

	1	2	3	4	5	6	7	8	9	10
(1) VO_2 max	—									
(2) Lactate	**.177***	—								
(3) Norepinephrine	.004	−.040	—							
(4) Temperature	.033	**.214****	.047	—						
(5) HR	**.434****	**.429****	−.094	**.172***	—					
(6) SBP	**.193****	**.208****	.047	.078	**.185***	—				
(7) RPE	**.157***	.117	−.039	.014	**.231***	.048	—			
(8) PA	−.038	−.125	**.174***	.060	−.071	−.024	−.036	—		
(9) FS$^{\pm}$	−.017	**−.173***	.086	**.149***	−.054	−.071	**−.163***	**.455***	—	
(10) Pain	−.023	**.215***	**−.165***	.000	.109	.108	**.316****	−.028	−.129	—

Note: $^*P < .05$, $^{**}P < .01$, $^{\pm}$Higher numbers indicate a more positive feeling state; All of the variables listed within this table are represented as change scores (VO_2 max excepted). Change scores were created by subtracting baseline values from values recorded at 30 minutes into the exercise bout. PA: positive affect; FS: feeling scale (affective valence).

such that for rs2253206, individuals with the G allele had higher VO_2 max, and for rs2360969, individuals with the C allele had higher VO_2 max. The *OPRM1* SNP rs1799971 was significantly associated with lactate change during exercise (r = .17, P =.02), norepinephrine change during exercise (r = .16, P = .03), and change in RPE during exercise (r = .14, P = .048), indicating that individuals with the rare G allele had greater changes in lactate, norepinephrine, and rate of perceived exertion change over the course of exercise. The *FTO* SNP rs8044769 was related to change in positive affect during exercise (r = −.16, P = .03), and individuals with the C allele had greater change in positive affect over the course of the exercise. The *FTO* SNP rs3751812 was associated with positive affect change during exercise (r = .14, P = .04), such that individuals with the T allele experienced greater changes in positive affect. The *FTO* SNP rs9941349 was significantly related to change in systolic blood pressure during exercise (r = .15, P = .04), and individuals with the T allele experienced greater increases in systolic blood pressure during exercise. The *FTO* SNP rs7201850 was significantly related to change in systolic blood pressure during exercise (r = .17, P = .027), with individuals possessing the T allele experiencing greater increases in systolic blood pressure over the course of the exercise bout. The *SLIT2* SNP rs1379659 was associated with norepinephrine change during exercise (r = .18, P = .01), with individuals with the G allele experiencing greater changes in norepinephrine during exercise. Finally, the FAM5C SNP rs1935881 was associated with change in norepinephrine during exercise (r = −.16, P = .03). Individuals with the G allele had greater changes in norepinephrine over the course of the exercise bout (All associations initially reported in the manuscript changed only slightly after applying the PCA correction. PCA corrected p-values for genotype-phenotype associations are as follows: rs1799971 and norepinephrine change (P = .104), rs1799971 and RPE change, (P = .038), rs8044769 and positive affect change (P = .038), rs3751812 and positive affect (P = .036), rs1935881 and norepinephrine change (P = .059), rs1379659 and norepinephrine change (P = .010), rs9941349 and systolic blood pressure change (P = .053), rs7201850 and systolic blood pressure change (P = .04998), rs2360969 and temperature change (P = .031), rs2253206 and temperature change (P = .066), rs1799971 and lactate change (P = .015), rs2253206 and VO_2 max (P = .035), and rs2360969 and VO_2 max (P = .032)) .

Due to the fact that several of the variants that were associated with a particular phenotype were in the same gene, it is likely that these SNPs are in high-linkage disequilibrium with one another. These SNP sets within single genes are rs3751812 and rs8044769 in FTO, both significantly associated with positive affect change, rs2253206 and rs2360969 in CREB1, both significantly associated with temperature change as well as VO_2 max, and rs7201850 and rs9941349, both in FTO, both significantly associated with systolic blood pressure change. To examine whether these SNPs were in LD, we ran correlations on each set of 2 SNPs in the same gene that were associated with the same phenotype. The correlation between rs2360969 and rs2253206 was .805 (P < .01), the correlation between rs3751812 and rs8044769 was −.676 (P < .01), and the correlation between rs7201850 and rs9941349 was .938 (P < .01).

In order to further explore the direction of the relationship of genotype on exercise response, we graphed the adjusted means for each genotype of three SNPs which demonstrated particularly robust relationships with exercise response phenotypes. We graphed the relationship between rs2360969 and temperature 30 minutes into the exercise bout, between rs1799971 and RPE 30 minutes into the exercise bout, and between rs8044769 and positive affect score 30 minutes into the exercise bout. As can be seen in Figure 1, individuals with the TT genotype of rs2360969 showed the highest temperature after 30 minutes of aerobic exercise, controlling for baseline temperature. In Figure 2, we show that individuals with the AG/GG genotypes on rs1799971 show greater RPE after 30 minutes of aerobic exercise than individuals with the AA genotype, controlling for baseline RPE. In Figure 3, we show that individuals with the CC genotype in rs8044769 show the highest ratings of positive affect after 30 minutes of aerobic exercise, controlling for baseline positive affect.

4. Discussion

The present study replicated prior findings suggesting that SNPs in the *CREB1, FTO, OPRM1, SLIT2*, and *FAM5C* genes are all related to phenotypes encompassing various responses to exercise. Our study tested conceptually relevant phenotypes that to date had not been explored in this way inany other exercise research. Given that the physiological response to aerobic exercise involves a complex interplay of metabolic, cardiovascular, musculoskeletal, ventilator, and hormonal functions [46], these genes and SNPs are likely to explain only a small portion of the variability in individual differences in response to aerobic exercise. Subjective responses to exercise may be yet more complex, involving sociocultural factors, effects of previous exercise experiences, and anticipated consequences/rewards of exercise [47]. Additionally, our findings suggest that individuals performing equivalent bouts of aerobic exercise may have vastly different subjective perceptions of this exercise (overall experiences which can range from negative to positive), and that these perceptions may be influenced by genotype. Giving sedentary individuals information about their propensity to respond to exercise in a particular way could provide useful insight, allowing these individuals to temper their expectations of what aerobic exercise "should" feel like for them or allowing intervention designers to incorporate external reinforcement contingencies (e.g., social interaction) for individuals who are less likely to experience intrinsic rewards from exercise.

Despite several inherent limitations, the present study's findings linking genetic variants to exercise responses among sedentary individuals presents promising initial evidence associating genes and exercise behavior. However, it is unlikely that variation at a single genetic locus could fully explain variation in physiological and subjective responses to exercise—more possibly, there are many genetic variables

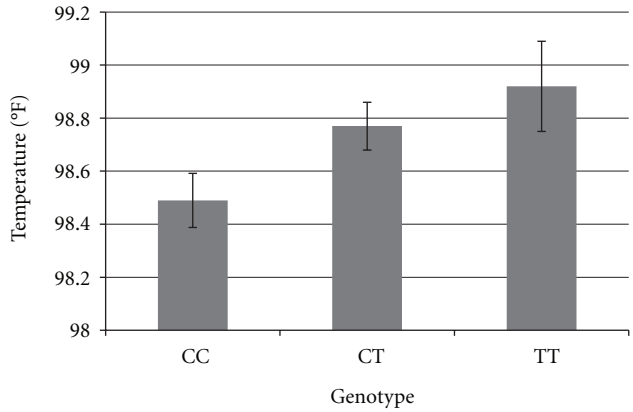

Figure 1: Adjusted mean temperature 30 minutes into the exercise bout, for individuals in each genotype of rs2360969 controlling for baseline temperature.

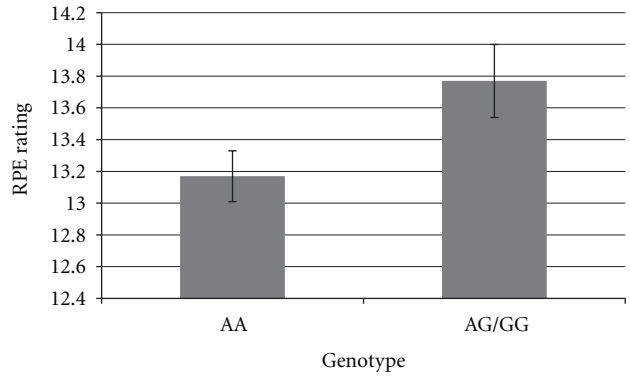

Figure 2: Adjusted mean rating of rate of perceived exertion 30 minutes into the exercise bout, for individuals in each genotype of rs1799971, controlling for baseline RPE rating. Individuals in the GG and AG group were combined, due to low *n*, for the GG group.

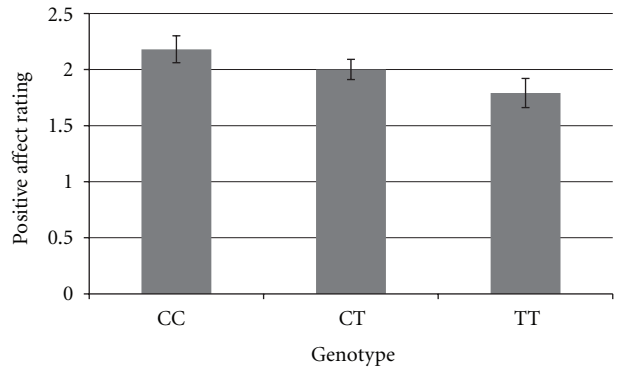

Figure 3: Adjusted mean rating of positive affect 30 minutes into the exercise bout, for individuals in each genotype of rs8044769, controlling for baseline positive affect rating.

influencing this phenotype, each of which contributes only by a small fraction of the observed variation [48]. When combined into a genetic composite, these loci would likely correlate more strongly with phenotypic response. So, although the correlations between genotype and exercise response found in this study are not large, they represent a necessary first step in forming genetic composite scores that are likely to be more highly correlated and significantly predictive of exercise responses. In summary, linking SNPs to specific physiological and psychological mechanisms that contribute to exercise response will assist in informing individually tailored exercise programs, as well as deepen our understanding of the relationship between genetics, physiology, and psychology underlying health behaviors associated with cancer prevention.

4.1. FTO. Our study showed that for rs3751812, the presence of a T allele increased change in positive affect during exercise. This finding is somewhat at odds with previous work suggesting that TT individuals have higher BMI on average. Rs3751812 was found to have a strong association with BMI in African-derived populations, with the TT genotype predicting increased BMI [49]. However, the relationship between BMI and positive affective response to exercise is unclear because the Hassanein study [49] did not include information about exercise behavior of participants. It is possible that rs3751812 individuals are predisposed to have higher BMI, but if they engage in aerobic exercise, they are likely to have a more positive affective response. This is one example of how knowledge about the effect of a particular genotype could be used to prescribe tailored interventions—for overweight individuals with the TT genotype, exercise could be recommended as a more effective weight loss tool, given that these individuals have a more positive affective response to exercise.

We also found that for rs8044769, the TT individuals had greater changes in positive affect during exercise. In a Hispanic American sample, rs8044769 was found to be weakly associated with waist-to-hip ratio [50], and the C allele showed an association with variation in BMI [51]. Additionally, an association was demonstrated between rs8044769 and pediatric BMI [52]. Prior research suggests that the C allele of rs8044769 is associated with greater *variation* in BMI [51]. This SNP seems to be related to body fat mass, predisposition to obesity, and response to aerobic exercise—yet the nature of this relationship requires further exploration. Associations between this SNP and additional obesity-related phenotypes should be tested.

4.2. CREB1. *CREB1* is a key component of long-term cardiac memory formation (specific T-wave patterns on an electrocardiogram) [53], as well as long-term memory formation in the brain [54, 55]. Our results indicate that for the *CREB1* SNP rs2253206, individuals with the A allele (AG genotypes, and to a greater extent AA genotypes) have a greater change in temperature during exercise. If greater temperature change while exercising translates into a more unpleasant subjective exercise experience, then our findings suggest that the AA individuals (and to a lesser extent AG individuals) may have less pleasant subjective experiences of exercise than GG individuals. rs2253206 was shown to be strongly associated with heart rate (HR) change in response

to a 20-week endurance training program, with GG and AG genotypes and showing 57% and 20% better change in HR than the AA participants [38].

Our results make sense in the context of the Rankinen findings [38], as the AA individuals may have more unpleasant exercise experiences due to increased temperature, which could influence their ability to exercise effectively (and thus decrease the heart rate improvements they can obtain from an exercise intervention). We also found that this SNP was related to VO_2 max (an indicator of cardiovascular fitness), such that the GG individuals had greater VO_2 max than AG individuals, who had greater VO_2 max than AA individuals. These results also coincide with our findings and the findings from previous research, as GG individuals may be more fit to begin with, and also more capable of gaining increased fitness through training, due to the fact that they experience exercise as less painful.

Additionally, we found that for rs2360969, TT individuals experienced greater change in temperature than did CT and CC individuals. rs2360969 has also been shown to be related to heart rate response endurance training [38, 39], however, these studies did not state direction of effect for this SNP.

4.3. OPRM1. In our analysis, rs1799971 (the A118G polymorphism) was related to RPE, as well as to lactate change during exercise and norepinephrine change during exercise. For all three of these phenotypes, individuals with the rare G allele showed greater change during the exercise bout. Previous research on this SNP has found that individuals with the G allele (genotypes of either AG or GG) demonstrated higher pressure pain thresholds than individuals with the AA genotype [36]. This study also found that when heat pain was tested, a sex by genotype interaction emerged, such that the G allele was associated with lower pain ratings among men but higher pain ratings among women. The A118G variant has greater binding affinity for β-endorphin (an exogenous opioid that activates the mu opioid receptor) [56], which is one possible mechanism by which this SNP could influence pain sensitivity.

The relationship between rs1799971 and subjective responses to pain may extend to the pain and exertion experienced during aerobic exercise. Given that our sample was 79.5% female, our findings of greater lactate, norepinephrine and RPE change over the course of exercise for the GG/AG group is in the same direction as the findings for females in the Fillingim [36] study. These results lend further support to the idea that individuals (and perhaps particularly women) with the AG/GG genotype have lowered pain threshold, and the present study suggests increases in lactate and norepinephrine as possible physiological explanations, at least in the context of aerobic exercise-induced pain.

4.4. FAM5C. Prior studies have shown that rs1379659 in *FAM5C* is associated with echocardiographic traits, and specifically left ventricular systolic dimension. The results of our study suggest that it is also associated with change in norepinephrine in response to exercise. To date, research has not examined the relationship between *FAM5C* and aerobic exercise response. Given the connection between this gene and cardiac function, examining the potential relationship between *FAM5C* and aerobic exercise would provide a logical next step for research in this area.

4.5. SLIT2. Previous research has demonstrated an association between the *SLIT2* SNP rs1935881 and echocardiographic traits, specifically left ventricular diastolic dimension. The results of this study suggest that it is also related to norepinephrine change during exercise. Further research is needed to elucidate more specific relationships between *SLIT2* and response to aerobic exercise.

The genes discussed above represent potential candidates for further explanation in terms of their relationship to exercise response phenotypes. More than a decade's worth of research on the psychophysiological responses associated with exercise has demonstrated that the subjective experience of exercise, how sensations are remembered, anticipated, and interpreted, is closely tied to subsequent exercise behavior [14, 19, 20, 47, 57]. A better understanding of the genetic basis for subjective responses to aerobic exercise may have the potential to lead to more effective and sophisticated intervention designs. Eventually, these advances in the basic science of exercise response could lead to the implementation of interventions tailored on the level of individual genetic variants.

Primary prevention of cancer through behavioral intervention is now a top priority of the NCI. This approach is intuitive given that approximately 30% of total cancer deaths are related to energy imbalance (e.g., excessive adiposity) [58, 59]. Physical inactivity is not the only contributing factor to energy imbalance, but it is a major contributing factor as trends clearly show that the least physically active regions of the country are also the most obese [60]. The hopeful perspective on behavioral intervention for physical activity is that even small increases in the total amount of participation accumulated per week stands to lead to meaningful differences in cancer risk. For example, [61] found evidence for a 3–8% reduction in risk for breast cancer with every additional 60 minutes of physical activity engaged in per week.

The link between physical activity participation and reduced risk for cancer, especially of the colon, breast, and endometrium is convincing, but also dependent upon good adherence [3–6, 61]. For this reason, it is imperative that researchers continue to search for ways to improve the likelihood of adherence to behavioral interventions. One way to achieve this goal may be through increasing the amount of focus that is placed on subjective response phenotypes and their underlying genetic variants. Developing a better understanding of the link between genes, exercise-relevant physiological mechanisms, and the resulting exercise-response phenotypes is a first step towards tailoring individualized exercise programs that would likely increase adherence and lead to improved health outcomes and decreased rates of cancer and other diseases.

4.6. Limitations. As with all research that involves genetic analyses, we cannot rule out the possibility that other genetic factors, including rare or common SNPs, insertions, deletions, or copy number variants, could play a role in determining the physiological responses to exercise that were measured in this study [48]. The phenotypes investigated in this study are likely to be polygenic traits, such that numerous genes and SNPs other than those examined in the present study may all contribute to these exercise response phenotypes. In contrast, the extent of the pleiotropic effects of the genes and SNPs investigated in this study are unknown. Thus, it is possible that the polymorphisms that influence exercise response may also be more strongly associated with other, possibly unrelated phenotypes that led to our findings [21].

Another limitation of note is the present study's lack of power to detect moderation effects of demographic variables. It is possible that variables such as age or ethnicity could moderate the associations between genetic variation and response to exercise. Further research should focus on testing these associations among different racial and age groups. Additionally, the results of this investigation are based on one single, standardized, bout of moderate-intensity exercise. For this reason, our results cannot be generalized to subjective exercise experiences that occur under less regulated circumstances (i.e., when type of activity, intensity, and duration are individually determined). Despite this limitation, there are many examples from the literature in which subjective responses to exercise are measured and analyzed based on a single bout of standardized exercise (e.g., [19, 20, 62–65]) and therefore, our procedures and analyses are in concert with the approach previously established by the field. Importantly, the purpose of the present investigation was to understand how genetic variants are associated with particular subjective responses to exercise when the parameters of the exercise experience are standardized across all individuals. In the present study, this level of standardization was achieved by having all participants perform the same activity (treadmill walking), for the same duration (30 minutes), at the same intensity (65% of each individual participant's previously established VO_2 max). Further, efforts were made to standardize variables external to the exercise bout as well (i.e., instructions detailing recommended calorie and water consumption prior to the bout described in Section 2). It remains to be seen whether the SNPs and genes reported in this study to be related to exercise response phenotypes would show an association to these same phenotypes in other studies examining different types, duration, and intensity of exercise sessions. Further, there may be some effect of population substructure in these associations. However, as noted, the size of the associations changed negligibly after a PCA correction, suggesting that the population substructure did not play a major role. Overall, replication is needed in order to confirm findings from the present study, and to better understand the functional significance of these genes and SNPs in relation to physiological and subjective responses to aerobic exercise.

5. Conclusion

The purpose of this paper was to explore the genetic underpinnings of individual physiological and subjective responses to aerobic exercise. One strength of this study was its focus on a sedentary population, a group that has been rarely tested in terms of associations between genetics and exercise phenotypes. The relationship between particular genetic variants and responses to exercise has important implications for the prevention of cancer via increasing exercise behavior in sedentary populations. Future studies designed to test genetic influences on a wide range of exercise response phenotypes would help to advance this goal, potentially leading to a panel of markers important for characterizing the physiological and subjective response to exercise. Moreover, giving feedback to sedentary individuals regarding the genetic basis for their strengths and weaknesses in fitness/exercise/sports activities could be a potentially useful motivational tool for increasing exercise behavior [13, 66]. In sum, expanding our understanding of the association between genetics and exercise response phenotypes has a myriad of implications for helping to increase exercise behavior in sedentary individuals, an outcome which is crucially important for the reduction of morbidity and mortality associated with cancer.

Conflict of Interests

The authors declared that no conflict of interests exist.

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Research Article

Screening and Health Behaviors among Persons Diagnosed with Familial Adenomatous Polyposis and Their Relatives

Aimee S. James,[1] Phillip Chisholm,[2] Kathleen Y. Wolin,[1] Melanie Baxter,[3] Kimberly Kaphingst,[1] and Nicholas O. Davidson[4]

[1] *Division of Public Health Sciences, Department of Surgery, Washington University in Saint Louis, 660 So. Euclid Avenue, P.O. Box 8100, Saint Louis, MO 63110, USA*
[2] *Department of Medicine, Washington University in Saint Louis, 4950 Children's place St. Louis, MO 63110, USA*
[3] *Siteman Cancer Center, Washington University in Saint Louis, 660 So. Euclid Avenue, P.O. Box 8100, Saint Louis, MO 63110, USA*
[4] *Division of Gastroenterology, Department of Medicine, Washington University in Saint Louis, 660 So. Euclid Avenue, P.O. Box 8124, Saint Louis, MO 63110, USA*

Correspondence should be addressed to Aimee S. James, jamesai@wudosis.wustl.edu

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Familial Adenomatous Polyposis (FAP) is a rare autosomal dominantly inherited colorectal cancer syndrome. Individuals with FAP often undergo colectomy and are recommended to follow several surveillance protocols. Biological relatives of persons with FAP may also be at risk and thus should undergo genetic counseling. Screening adherence, genetic testing, and other health behaviors among individuals with FAP and their relatives are not well characterized. We conducted a cross-sectional self-report survey with individuals who have FAP ($n = 35$) and their biological relatives ($n = 15$). Respondents were recruited through a cancer center registry for inherited colon cancers. Most relatives had undergone colon cancer screening; 40% had undergone genetic testing. One fifth of respondents with FAP had not undergone an upper endoscopy, contrary to usual recommendations. Cigarette smoking rates were above average and were higher among FAP respondents. Use of vitamin supplements was fairly common, more so among those with FAP. Although most people had been screened, there are areas for improvement, notably for upper endoscopy among individuals with FAP and genetic testing among family members. Several other health-risk behaviors and health concerns other than FAP were identified. Further research into factors contributing to screening rates and other health behaviors in this high-risk population is warranted.

1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer deaths in the United States [1]. About 30% of CRC cases are associated with family history or inherited factors and 5% are attributed to well-identified inherited gene mutations [2]. Familial adenomatous polyposis (FAP) is a highly penetrant autosomal dominant colon cancer syndrome and is the second most common genetic CRC syndrome. The reported incidence of FAP varies from 1 in 6,000 to 1 in 22,000 individuals [3–5]. Individuals who have FAP often develop hundreds to thousands of colorectal adenomatous polyps and have a near 100% risk of CRC in the absence of clinical intervention. Thus, most patients with FAP undergo either a complete or subtotal colectomy in young adulthood and are recommended to continue surveillance for extracolonic manifestations such as duodenal and periampullary carcinomas and papillary thyroid cancer. Screening and surveillance protocols vary depending on several factors including the severity of the disease and its type (classic or attenuated FAP), previous surgery, and type of surgery [6].

FAP is associated with mutations in the adenomatous polyposis coli (APC) gene, which results in development of numerous polyps. While FAP is inherited as a highly penetrant autosomal dominant syndrome, up to a third of patients do not have a family history of FAP and may represent a new (de novo) mutation [7]. When a familial-specific mutation can be identified in a patient, it allows

other family members to be tested, often before any clinical manifestations of disease. Unfortunately, not all FAP patients have an APC gene mutation that can be found; individuals with the greatest polyp burden (e.g., more than 100 polyps) are more likely to have an identifiable APC gene mutation [7–9]. As with many other inherited colorectal cancer syndromes, genetic counseling is strongly recommended for patients and their biologic family members. Studies estimate that uptake of genetic testing in patients with FAP varies widely, and up to 40% of individuals may not be tested [10, 11].

Individuals diagnosed with FAP or at risk for FAP, like those affected by other inherited CRC syndromes, are expected to adhere to a number of screening recommendations. Protocols for postsurgical lower endoscopic surveillance depend on the type of surgery performed but include annual endoscopic surveillance of remnant anorectal tissue [6]. Yearly checkups with a physician should be opportunities to screen for other, extraintestinal complications [12]. Because of the increased risk for duodenal and periampullary cancers, screening of the upper gastrointestinal tract through upper endoscopy should occur periodically, depending on the size, histology, and number of polyps.

Endoscopic screening rates may be low, however. Suboptimal rates for CRC screening have been documented in the general population and among patients at high risk due to family history or inherited conditions [13–18]. For example, individuals with or at-risk for Lynch syndrome, another inherited colorectal cancer syndrome, may be nonadherent to screening recommendations [17, 19]. Nonadherence takes the form of both hypovigilance (i.e., underscreening) or hypervigilance (i.e., overscreening), but among people undergoing genetic testing for Lynch syndrome, screening behaviors were associated with knowing one's mutation status. In general, screening frequency decreases after testing mutation negative [18], but nonadherence may be particularly concerning for individuals whose Lynch syndrome genetic testing is inconclusive [20]. However, only a handful of studies have examined screening and surveillance specifically among individuals who have FAP and their family members [15, 21]. One previous study in the USA reported that slightly more than half of participants who had an FAP diagnosis had recent colorectal screening; rates were lower for at-risk relatives, suggesting underscreening [16].

Individuals with an inherited CRC syndrome and their relatives remain at risk for other cancers, common chronic diseases, and complications from their disease. A number of health behaviors have been associated with increased risk for CRC and cancer in general, such as cigarette smoking and dietary factors and supplements. Screening for other cancers, such as breast and prostate, may also be important for health promotion. These behaviors may be influenced by the reality of living with FAP, increased cancer risk, or associated with other chronic conditions (e.g., diabetes) that themselves increase risk for CRC. Burton and colleagues reported that among individuals at risk for Lynch syndrome, cancer screening rates were similar to those for the general population, but that health-risk behaviors were more common among individuals with CRC than among those who tested negative for the syndrome [19]. The prevalence of these health behaviors (or health-risk) behaviors has not, to our knowledge, been characterized in a published research study of FAP kindreds.

We were interested in ascertaining the needs of individuals with FAP and their relatives in regard to health behavior, disease management, health information, and how needs might be affected by having an inherited CRC syndrome. To build a foundation for future research, we conducted a cross-sectional survey to explore rates of health/health-risk behavior, use of genetic testing, comorbid chronic diseases faced by families, and understanding of genetics and their illness.

2. Methods

2.1. Study Overview. This was a single-center cross-sectional survey study of patients with FAP and their biological relatives. Participants were recruited from a cancer-center based registry of patients with known inherited colon cancer syndromes. Respondents completed a survey and were asked to invite family members to complete a survey as well.

2.2. Participants and Recruitment. Eligible participants were 18 years of age and older, able to speak or understand English, and had a diagnosis of FAP or were related to someone with FAP. There were no additional exclusion criteria. All members of the cancer center's inherited colorectal cancer registry who had been diagnosed with FAP (or were a biologic relative) and had previously provided consent to be contacted for future research studies were mailed an invitation letter and information sheet about the study. A follow-up telephone call was made within two weeks of the mailing. The research team attempted telephone contact at least five times, varying day and time, to maximize the opportunities to reach the registrant. The purpose of the telephone call was to prompt survey completion and answer any questions the individual may have had. If registrants had an email address on file with the registry, invitations were sent by electronic mail.

2.3. Procedures. The invitation letter contained instructions and a password for access to the internet version of the survey. Although the survey was designed to be completed via the internet, participants who were reached by telephone and had not yet completed the survey online were offered the opportunity to complete the survey by telephone. If requested, paper versions of the survey were mailed. The survey took about 30 minutes when completed over the telephone. Participants provided verbal consent and did not receive a monetary incentive. Survey responses were not linked to medical information in the registry. Data were collected over a five month period between November 2010 and April 2011. All procedures and materials were approved by the University's Institutional Review Board.

2.4. Measures. Our survey items were selected to address key areas that our multidisciplinary research team thoughts were

important for health and wellbeing of individuals with FAP and their family members based on a review of the FAP and colon cancer clinical and epidemiological literature. These included comorbid conditions and health status, health behaviors and cancer screening, and several FAP-specific constructs (e.g., knowledge). All items were self-reported. Most questions were the same for patients with FAP and for relatives, but some were adapted per FAP status or were only asked of those who had FAP.

Demographic and Health Status. Demographic factors assessed included age, sex, race/ethnicity, household income, employment status, marital status, and health insurance; these items were measured using standard questions from national health surveys. We also assessed years of education attained. Health status items included comorbid chronic conditions (e.g., diabetes, hypertension, heart disease) and self-rated health. An open-ended question asked respondents to free list their top health concerns.

Health Behavior and Cancer Screening. Respondents were asked about vaccination for pneumonia (lifetime) and influenza (current season), daily consumption of fruits and vegetables per day, current use of nutritional supplements, and cigarette smoking (current and ever). Participants were asked about CRC screening including fecal occult blood testing, sigmoidoscopy, and colonoscopy, using validated questions [22]. For each screening question, participants were provided a description of a screening test and asked if they had ever had it, and, if yes, when they had their most recent test. Using a similar format, women were asked about mammography and cervical screening and men were asked about prostate specific antigen testing.

FAP-Specific Questions. FAP patients self-reported details of their disease and treatment, including surgeries, patient-provider discussion about FAP and risk, genetic counseling, genetic testing, and outcomes of genetic testing. Additionally, participants were asked about their awareness of family members with cancer or FAP, including how many total relatives were known to be affected and their relation. Finally, participants were asked about cancer-related worry and FAP knowledge.

2.5. Analysis. Data analyses were conducted using SPSS software. Descriptive statistics are reported, stratified by FAP status. Due to the small sample size, we did not test for significance. Values were not adjusted for the potential clustering in the data due to having multiple respondents from the same family.

3. Results

3.1. Sample Description. We mailed invitation letters to all eligible registry members ($n = 66$). Of those, 40 completed surveys, 11 did not complete the survey, 1 declined participation, and 14 were not reached. We asked respondents to invite additional biological family members (who were at least age 18) to participate; additional 10 respondents were accrued through this strategy. In total, our sample ($N = 50$) consisted of 35 respondents with a known FAP diagnosis, and 15 of their relatives. FAP status of relatives was either negative or unknown. About half of respondents ($n = 26$) completed the survey online, 12 chose telephone interviews, and 12 returned paper surveys. Most respondents (62.0%) were female and nearly all (94.0%) self-identified as White. Few demographic differences were evident between respondents with FAP and relatives (see Table 1), but 65.7% of those with FAP were married or living with a partner, compared to 80% of relatives.

3.2. Colon and FAP-Related Screening and Surveillance. Most relatives of patients with FAP had undergone a colonoscopy within the past 5 years (87.5% of those aged 50 and over). Relatives said that they had talked with a doctor about FAP (80% said yes) and had a doctor explain their risks due to being in an FAP family (66.7%) and their personal risk for CRC (80.0%). Forty percent of relatives had undergone genetic testing for FAP.

All respondents who had FAP had undergone a colonoscopy at some point in their lives, 62.9% of which occurred in the previous five years. Despite strong recommendations for regular upper endoscopic screening, 20% of respondents with FAP had either never had upper endoscopy or were unsure. Most of the respondents with FAP had undergone genetic testing (60.0%) and knew of other family members who had been tested (65.7%).

3.3. Knowledge and Attitudes about FAP and Cancer. Perceived risk of CRC varied greatly amongst relatives, with one-fifth of respondents perceiving very high risk and one-fifth perceiving very low risk. While perceived risk varied but was high for many people, colon cancer worry was generally low. Most respondents (60.0%) said they "rarely" or "never" worried about getting CRC. Further, relatives endorsed positive attitudes about colon cancer prevention and felt they understood the recommendations; with the majority disagreeing with the statements that "there is not much you can do to lower your chances of getting colon cancer" (73.3% disagreed) and "there are so many recommendations about preventing cancer, it is hard to know which to follow" (66.7% disagreed).

On the other hand, among relatives, there was some misunderstanding about FAP genetics. A majority (66.7%) responded that children who do not inherit FAP can still pass it on to their own children, and 40% were not sure of the likelihood that a child would inherit the disease from a parent with FAP.

3.4. Health and Other Health Behaviors. Table 2 describes health status and health behaviors among respondents. Although most respondents characterized their health as "good" (44.1% of FAP, 40.0% of relatives), there were some differences between those with FAP and their relatives. In particular, 35.3% of patients with FAP self-rated their health as "excellent" or "very good" compared to 46.6% of relatives.

Table 1: Demographic characteristics of the sample ($N = 50$).

Characteristic	Total sample $N = 50$ % (N)	FAP-only $n = 35$ % (N)	Relatives $N = 15$ % (N)
Gender			
Female	62.0% (31)	65.7% (23)	53.3% ($n = 8$)
Race/ethnicity			
White or Caucasian	94.0% (47)	94.3% (33)	93.3% ($n = 14$)
Income level			
< $34,999/year	42.5% (20)	42.4% (14)	42.9% (6)
Employment status			
Full time	44.0% (22)	42.9% (15)	46.7% (7)
On Disability	14.0% (7)	17.1% (6)	6.7% (1)
Marital status			
Married or living with a partner	70.0% (35)	65.7% (23)	80.0% (12)
Health insurance			
Insured, including Medicare or Medicaid	88.0% (44)	93.9% (31)	86.7% (13)
Known family history of cancer,			
Yes	88.0% (44)	91.4% (32)	80.0% (12)
	Mean (Range)	Mean (Range)	Mean (Range)
Age			
(Mean (range))	50.2 (23–75 years)	50.8 (23–75 years)	48.8 (25–70 years)
Health care			
Past year, mean number of visits (range)	8.3 (0–35 visits)	10.4 (0–35)	3.6 (0–14)

Values represent valid percents. Responses include yes and "not sure."

One-fifth (20.6%) of those with FAP rated their health as "fair" or "poor" compared to 13.3% of relatives.

Preventive care and other screening utilization were consistently high in this sample. Nearly all women age 40 and older had ever had a mammogram (95.7%), many within the past year (60.9%). Cervical cancer screening rates were similarly favorable (96.8% ever screened; and 80% screened with the last three years). Mammography and Pap testing rates were similar between FAP and relative respondents. Flu and pneumonia vaccination reports were higher among those with FAP (64.7% received the current flu season shot, 28.6% ever had pneumonia vaccine) than among the relatives (40.0% flu shot, 20.0% pneumonia).

Given the shared risk factor profiles of colon cancer and several chronic diseases, we also assessed the presence of other chronic conditions. Half of respondents reported another chronic condition; the overall prevalence did not appear to differ between those with FAP and their relatives. The most commonly reported conditions included high blood pressure (42.9% of FAP, 46.7% of relatives), and diabetes (20.0% of FAP, and 7.1% of relatives). Cigarette smoking rates were higher among the respondents with FAP. Among those with FAP, 28.6% were current smokers, and another 34.3% had previously smoked but had quit more than 6 months prior. Among relatives, 21.4% were current smokers, and 35.7% had quit more than six months prior. Most respondents reported eating two or fewer servings of fruits and two or fewer servings of vegetables each day. Supplement use was higher among those with FAP compared to relatives, including use of Vitamin C (21.9% of FAP, 6.7% of relatives), Vitamin E (15.6% of FAP, 7.1% of relatives), and Vitamin D (36.4% of FAP, 3.6% of relatives). Sixty percent of those with FAP and 40.0% of relatives reported daily aspirin use. One exception to this trend was calcium supplements, which was higher in relatives (33.3%) than among those with FAP (21%).

4. Discussion

This is one of a few studies to examine screening and other health behaviors among individuals with FAP and their biological relatives. FAP is a rare, but well-characterized and prototypical autosomal dominant cancer susceptibility syndrome. The health behaviors of individuals with FAP or their family members have not been well characterized, although it is widely acknowledged that regular screening and surveillance are important for maximizing disease-free survival. Health risk behaviors such as cigarette smoking can detract from overall well being and increase risk for many cancers.

As other studies have found in inherited CRC syndromes [17], many respondents in our sample were vigilant about CRC screening. Screening rates were relatively high in the relatives of FAP patients in this sample—nearly 90% of those

Table 2: Preventive care and health behaviors of respondents with FAP and their relatives.

Characteristic[1]	Total Sample $N = 50$ %, (N)	FAP-only $n = 35$ % (N)	Relatives $n = 15$ % (N)
Self-rated health			
Excellent or Very good	38.8%(19)	35.3%(12)	46.6% (7)
Good	42.9%(21)	44.1% (15)	40.0% (6)
Fair or Poor	8.2% (4)	20.5% (7)	13.3% (2)
Co-morbidities[1]			
Heart disease	16.7% (8)	17.1% (6)	15.4% (2)
Diabetes	16.3% (8)	20.0% (7)	7.1% (1)
High blood pressure	44.0% (22)	42.9% (15)	46.7% (7)
Any comorbidity	48.0% (24)	48.5% (17)	46.7% (7)
Cancer, personal history	28.0% (14)	34.3% (12)	13.3% (2)
Vaccination			
Flu shot	57.1% (28)	64.7% (22)	40.0% (6)
Pneumonia	28.0% (14)	28.6% (10)	26.7% (4)
Mammography[2]			
Ever had	95.7% (22)	94.1% (16)	100% (6)
Exam within past year	60.9% (14)	58.8% (10)	66.7% (4)
Pap test[3]			
Ever had	96.8% (30)	95.7% (22)	100% (8)
Exam within three years	80.6%(25)	82.6% (19)	75.0% (6)
PSA test[4]			
Ever had	90.0% (9)	100% (6)	75.0% (3)
Test within last year	80.0% (8)	83.3% (5)	75.0% (3)
Colonoscopy			
Ever had	94.0% (47)	100% (35)	80.0% (12)
50 and over		n/a	*100.0% (8)*
Within last 5 years	66.0% (33)	62.9% (22)	73.3% (11)
50 and over		n/a	*87.5% (7)*
Provider recommended CRC Screening			
Yes	70.0% (35)	74.3% (26)	60.0% (9)
Upper Endoscopy			
Yes, Ever had	64.0% (32)	80.0% (28)	26.7% (4)
Not Sure	6.0% (3)	5.7% (2)	6.7% (1)

[1] Responses combine yes and "not sure". [2] Women, age 40 and over (FAP $n = 17$; FDR $n = 6$). [3] Women, over age 18 (FAP $n = 23$, FDR $n = 8$). [4] Men, age 50 and over (FAP $n = 6$; FDR $n = 4$).

over 50 reported a colonoscopy within the past five years. Although the rate of recent colonoscopy appeared to be lower in FAP patients than relatives, this likely reflects the type of surgery the individual had received and the medical appropriateness of colonoscopy versus other strategies for surveillance of any remaining colon or rectum. We did not have the medical record data to determine what each person's optimal screening interval should be, so some of this may in fact reflect overscreening or misclassification of screening status. However, it should be noted that this rate is higher than has been reported in many studies of FAP kindred [15, 16, 21]. Future studies would benefit from the integration of medical record and patient reported data to better characterize screening adherence.

The relatively high rate of screening may also be reinforced by a high number of unaffected relatives who had discussed their family's history of FAP with a doctor, and the strong support by respondents for the benefits of screening. It may also be influenced by what seemed to be a lack of understanding of the genetics of FAP among relatives, specifically worries that the disease could still be passed down to children even when the parent has tested mutation

negative. This misconception has also been reported in Lynch syndrome [23]. The high level of interest in genetic testing for CRC [24] and associations between risk perceptions and genetic testing [25, 26], when combined with higher rates of cancer screening found in many studies, may reflect a need for reassurance of genetically "unaffected" individuals and a focus on genetic literacy by all health professionals who interact with individuals in families affected by FAP. On the other hand, some researchers have found that screening may decrease (either appropriately or to underscreening) after testing mutation negative for cancer syndromes [18]. Additional studies of genetic literacy [27–29] as well as lay theories of inheritance [30] might shed light on how individuals and families interpret—and cope with—their mutation status.

Other studies have identified higher-risk behaviors among individuals with a familial or genetic risk for CRC [19]. Particularly concerning in our study was the high rate of cigarette smoking (28.6% FAP and 21.4% relatives were current smokers). In comparison, 2010 data from the Behavioral Risk Factor Surveillance System for Missouri (our cancer center primarily draws patients from Missouri and neighboring states), indicate that 21% of adults statewide were current smokers. Respondents in our sample, therefore, smoked at rates equivalent to (for relatives) or higher than (for those with FAP) the statewide average, and much higher than the national average (17.2% current smokers). This is also equal to or higher than those rates reported for individuals with Lynch syndrome; Burton and colleagues reported that 29.1% of affected and 12.9% of unaffected patients were current smokers [19]. Cigarette smoking is a known risk factor for colorectal [31, 32] and other cancers, including those for which FAP also increases risk. Although the relationship between cigarette smoking and malignancy has not yet been investigated in FAP, studies of other inherited CRC syndromes have shown increased risk for polyps [33] or CRC [34] associated with smoking cigarettes. Thus, the seemingly high rate of cigarette smoking is concerning despite our small sample; such findings merit future investigation with larger FAP samples and biologic measurement.

Similarly, other behaviors or conditions that are generally associated with increased cancer risk in the general population, such as low fruit and vegetable consumption, were evident in our sample. Further, our data show that cancer is not the only health concern in this sample: heart disease, hypertension, and diabetes were also reported. In particular, diabetes was reported more often by FAP respondents. Much like the case with cigarette smoking, the potential that diabetes is more common among individuals with FAP may be important because of the increased adenoma [35, 36] and CRC risk [37–40] associated with diabetes, even though the link has not been specifically studied in FAP. We were unable to verify disease diagnosis or to explore disease management, or how FAP or a family history of FAP might interact with self-management for other conditions. The health promoting behaviors and concurrent chronic conditions among individuals with inherited CRC syndromes and their biologic relatives may be an important area to study, both in terms of identifying needs and potential interventions, but also examining care coordination and pathways to increased risk.

The data on supplement use in both those diagnosed with FAP and their biological relatives are novel and interesting. There is evidence for chemopreventive agents for CRC in average-risk and FAP patients [41]. There has been at least one published study of aspirin use in FAP patients demonstrating a reduction in polyp burden [42], and several good-quality studies have found a reduction in risk for recurrence of polyps, and the incidence of advanced adenomas and CRC with aspirin use in general [43–45]. In our sample, reported daily aspirin use was higher for FAP than non-FAP respondents, while both rates (60% and 40%) were fairly high. Other vitamin supplementation was relatively common (>15% of respondents with FAP answering yes). As far as we know, there are no studies of the impact of Vitamins C, E, and D in individuals with FAP [46], though some studies mention vitamin deficiencies [47] and avoidance of certain foods [48] after colectomy. So far, data on Vitamin D and calcium supplementation in the reduction of adenoma occurrence or the prevention of CRC has been suggestive but not conclusive [49]. The dosage, or whether supplementation was discussed with a clinical provider, is not evident from our data. However, the extent of supplement use, the reasons why patients seek out supplements, and the potential clinical implications warrant further study.

Our study is subject to some limitations. Respondents were drawn from a registry at the cancer center or were a biological relative of a registrant, and thus they may have more interaction with, or access to, specialists in FAP than would other FAP families. We were unable to link medical records to survey answers or verify self-reported diagnoses. Additionally, if our participants were seeing providers more often, there may be detection bias in their self-reported chronic conditions. The relatives in our study may also represent those family members closest to the person with FAP, or who were most receptive to health screening and discussion. This weakness is inherent in studies of kindreds affected by inherited syndromes, which primarily recruit clinically unaffected relatives through the patient. Thus, our rates of screening are probably higher than what we would find in a community-based sample of FAP kindred. Indeed, as we already stated, studies have reported higher rates of screening among individuals who are associated with polyposis or other inherited cancer registries. Although we cannot determine optimal screening intervals or strategies for respondents with FAP in our sample and our estimates for colorectal screening and upper endoscopy adherence are not tailored to the individual's risk, it is worth noting that all the participants who are in the registry are offered protocol-based screening (periodic upper and lower endoscopy). Our findings regarding chronic disease may be related to a detection bias if the patients saw a healthcare provider more often. Lastly, our sample size precluded advanced statistical testing, our descriptive analysis did not account for family-level variance or correlation, and we did not ask the relationship between patients and relatives.

5. Conclusions

Our findings in individuals with FAP and their biological relatives revealed relatively high rates of endoscopic screening, but some gaps in surveillance and screening, particularly with recommendations for upper endoscopy. There were also indications of lack of knowledge about FAP and its genetics and inheritance patterns.

These issues are relevant for other populations at high-risk because of genetic syndromes. There were some similarities between our health risk data and that reported elsewhere for other CRC syndromes. Clearly, patients and families affected by inherited syndromes are concurrently dealing with other chronic conditions (in this sample, most notably heart disease and diabetes), which may complicate their health-maintenance perceptions and behaviors. Additionally, much like other studies, we found a range of reactions among relatives including continued concern about FAP or its transmission. Patient-provider discussions about the genomics of disease could be targeted to address some of these concerns, and also widened to address *other* chronic conditions that might affect how individuals deal with their cancer syndrome.

Therefore, it is critical to characterize the prevalence and predictors of health and health behaviors among FAP kindred, and to explore how the increased risk associated with this syndrome may affect other behaviors and conditions. Additionally, future studies may try to extend the study sample beyond a cancer center or registry, in order to better capture the experience of FAP in the general population, and to combine patient-reported outcomes with objectively collected data.

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Research Article

Interpretation of Melanoma Risk Feedback in First-Degree Relatives of Melanoma Patients

Jennifer L. Hay,[1] Carlos Baguer,[1] Yuelin Li,[1] Irene Orlow,[2] and Marianne Berwick[3]

[1] *Department of Psychiatry & Behavioral Sciences, Memorial Sloan-Kettering Cancer Center, 641 Lexington Avenue, New York, NY 10022, USA*
[2] *Department of Epidemiology & Biostatistics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA*
[3] *Division of Epidemiology, University of New Mexico School of Medicine, University of New Mexico, MSC07-4025, 2703 Frontier Avenue, NW 190 RIB, Albuquerque, NM 87131-0001, USA*

Correspondence should be addressed to Jennifer L. Hay, hayj@mskcc.org

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Little is known about how individuals might interpret brief genetic risk feedback. We examined interpretation and behavioral intentions (sun protection, skin screening) in melanoma first-degree relatives (FDRs) after exposure to brief prototypic melanoma risk feedback. Using a 3 by 2 experimental pre-post design where feedback type (high-risk mutation, gene environment, and nongenetic) and risk level (positive *versus* negative findings) were systematically varied, 139 melanoma FDRs were randomized to receive one of the six scenarios. All scenarios included an explicit reminder that melanoma family history increased their risk regardless of their feedback. The findings indicate main effects by risk level but not feedback type; positive findings led to heightened anticipated melanoma risk perceptions and anticipated behavioral intentions. Yet those who received negative findings often discounted their family melanoma history. As such, 25%, 30%, and 32% of those who received negative mutation, gene-environment, and nongenetic feedback, respectively, reported that their risk was similar to the general population. Given the frequency with which those who pursue genetic testing may receive negative feedback, attention is needed to identify ideal strategies to present negative genetic findings in contexts such as direct to consumer channels where extensive genetic counseling is not required.

1. Background

The sequencing of the entire human genome in 2003 has led to a series of unrealized opportunities for public health benefit [1], many of which rest on accurate genetic risk interpretation and adoption of protective behavior [2]. By 2006, direct-to-consumer genetic testing and feedback was available through 24 Internet-based companies, many of which did not require physician or genetic counseling followup to ensure accurate interpretation of test findings [3]. Recent general population surveys indicate high levels of risk misinterpretation even among highly educated general population subgroups [4–6]. To date, the few studies that have examined outcomes associated with direct-to-consumer genetic testing have found no remarkable increases in distress, screening, or behavior change [7–9], yet it is unclear whether these findings may be due to risk misinterpretation, or lack of consideration of diverse elements of risk, including family history.

First-degree relatives (FDRs) of cancer patients may be among the first to pursue cancer genetic susceptibility testing through direct-to-consumer channels, given their heightened risk salience [10]. Among FDRs, interpretation of "negative findings"—the absence of an identified higher risk genetic risk variant—may present a particular challenge, because most of those tested will receive negative findings due to low population prevalence of risk mutations and common risk variants, and because it is unclear how negative genetic findings may be interpreted in the context of other relevant risk factors such as family history. LaRusse and colleagues [11] compared women's interpretation of genetic versus family history risk assessment "negative findings"

(identical 29% lifetime estimates of developing Alzheimer's disease) and found that those who received genetic risk feedback reported lower perceived risk and lower anxiety about developing the disease than those who received family history risk assessment. Accordingly, genetic test results indicating negative or uncertain findings may prove to be more salient and impactful than family history information, increasing the probability of diverse risk interpretations and continued information seeking [12, 13], variations in recall of test findings [14], and justifications for continued risk behavior [15].

To closely examine message interpretation and behavioral intentions given plausible genetic risk feedback, we examined these outcomes among individuals with a family history of melanoma. Melanoma is an ideal study context given the established genetic (high-risk mutations, as well as more common genetic variants) and environmental (ultraviolet radiation exposure) risks for this common cancer [16], and the need to enhance early detection and risk reduction strategies in melanoma FDRs [17]. This study employed an experimental pre-post design to assess message interpretation (aim I) and behavioral intentions (sun protection and skin screening, aim II) associated with receipt of hypothetical risk feedback modeled on varied prototypic melanoma genetic risk feedback in melanoma FDRs.

2. Methods

2.1. Participants. Melanoma FDRs ($N = 139$) participated in the study. With the approval of each patient's physician, 426 melanoma patients (English fluent, ≥age 18) were approached at their postsurgical followup appointments at Memorial Sloan-Kettering's (MSK) Gastric and Mixed Tumor Service by a research study assistant (RSA) who described the study, provided a brochure, and requested patients' assent to contact their eligible FDRs by telephone. Most patients (74%) stated initial willingness to refer an FDR when they were approached in clinic, and 66% of patients provided us with adequate referral information (name, relation to the patient, and telephone and contact information) for us to contact their FDR. Of the 280 FDRs who were referred, 50% participated ($N = 139$), 44% were unavailable by telephone after five attempts to reach them, and 6% refused participation. Those FDRs who participated did not differ in gender from those who did not participate. Study questionnaires were completed either by telephone or in clinic if the FDR was accompanying the patient. The sample was 70% female, 97% non-Hispanic white, highly educated (71% had a college degree) and mostly (78%) comprised daughters, sons, and mothers; all included participants were unrelated to each other. Few (8%) had more than one family member with melanoma; 14% had a personal melanoma history. Half (54%) had a sun-sensitive phenotype indicating skin prone to burning (skin type I/II; [18]). The study was approved by the MSKCC Institutional Review Board.

2.2. Design and Procedure. The study used a 3 by 2 experimental design where feedback type and risk level of the scenarios were varied, and participants were randomized to one of the six conditions. For feedback type, "*mutation feedback*" was modeled on inherited mutations in *CDKN2A* (gene encoding $p16^{INK4A}$), an identified tumor suppressor gene, that has been linked to hereditary melanoma (melanoma diagnosed in a family with two or more affected relatives; [19]). "*Gene-environment feedback*" was modeled on the melanocortin receptor gene (*MC1R*), which interacts with sun exposure to heighten population melanoma risk [20]. "*Nongenetic feedback*" was based on a nongenetic melanoma risk assessment that includes factors such as mole number [21]. Risk level was varied by whether the findings were positive (test identified higher risk genetic marker/nongenetic risk information) or negative. The RSA slowly reads one of six testing scenarios to each participant.

The following elements recommended by Persky and colleagues [22] were used to increase the accuracy of testing outcomes, including verbal elements to increase verbal immediacy of the scenario, use of a request to "imagine" they are having the test, the use of second person ("you"), a test administrator (nurse), a description of the test context in concrete terms, a description of each "new test" as immediately available, inclusion of detail about the tests (blood test, the heritability of melanoma, and the bases on which risk is determined for each test type), the use of a brief, relatively low text-dense scenario description, and finally random assignment to condition and slow, verbal presentation by the RSA.

All scenarios explicitly reminded participants that their melanoma family history raised their risk.

The information varying across conditions is presented in brackets:

> Please vividly imagine that you find yourself in the situation described below. Think hard about how you would feel and what you would think in this situation.
>
> Imagine that you learn from your doctor that there is a new test that will provide information about a person's risk of developing melanoma. [This genetic test involves giving a blood sample that is tested for a gene mutation that places a person at increased risk for developing melanoma/This genetic test involves giving a blood sample that is tested for a common genetic difference that makes someone more susceptible to the negative effects of sunlight and sunburn/This test involves a brief series of questions about whether you have had skin cancer before, freckling and number of large moles, how sun-sensitive you are, and sunburn history.] You know that as a close family member of someone who has had melanoma, that your risk is already increased, regardless of your test results. Imagine that you decide to take this test. [A nurse takes a sample of blood from you for this purpose (deleted for non-genetic feedback)]. Three days later you receive the test results. The results of the test are [positive/negative.]

Table 1: Scenario interpretation response frequencies ($N = 139$).

My test results indicate the following	Scenario version n (%)					
	Mutation positive	Mutation negative	GE positive	GE negative	Nongenetic risk positive	Nongenetic risk negative
My melanoma risk is unknown	0 (0.0)	1 (4.2)	0 (0.0)	1 (4.3)	0 (0.0)	3 (13.6)
I am certain to never get melanoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
My risk is decreased	0 (0.0)	8 (33.3)	0 (0.0)	7 (30.4)	1 (4.3)	9 (40.9)
My risk is not really different from the population	1 (4.2)	6 (25.0)	1 (4.3)	7 (30.4)	1 (4.3)	7 (31.8)
My risk is not really different from other people with a melanoma family history	4 (16.7)	9 (37.5)	6 (26.1)	4 (17.4)	5 (21.7)	1 (4.5)
My risk is increased	16 (66.6)	0 (0.0)	16 (69.6)	4 (17.4)	16 (69.6)	2 (9.1)
I am certain to get melanoma in the future	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Participants (% total)	24 (17.3)	24 (17.3)	23 (16.5)	23 (16.5)	23 (16.5)	22 (15.8)

GE: gene environment.

2.3. Measures of Test Comprehension and Behavioral Intentions

Pretest Assessment. Prior to scenario administration, we assessed perceived risk using established methods [23]. Accordingly, we assessed absolute verbal likelihood of developing melanoma ("How likely is it that you will develop melanoma in the future? Would you say your chance of getting melanoma is …" assessed on a 5-point scale, "very low" to "very high") and comparative likelihood of developing melanoma compared to same age and sex others ("Compared to the average person your age, would you say that you are …" assessed on a 3-point scale, "less likely to get melanoma," "about as likely to get melanoma," or "more likely to get melanoma"). Current self-reported sun protection practices (use of sunscreen, shirts, hats, shade seeking, and sunglasses when outside on a sunny summer day for more than an hour) were assessed on separate 5-point scales, "Never" to "Always," [24]. History of healthcare provider skin cancer screening and skin self-examination (history of prior screening, no history of prior screening) was also assessed.

Posttest Assessment. The posttest assessment was conducted immediately subsequent to scenario administration. Scenario interpretation was assessed two ways—through a multiple-choice item (see Table 1) and by a second administration of the same perceived skin cancer risk questions that were assessed at pretest [23]. Intentions for future sun protection practices (use of sunscreen, shirts, hats, shade seeking, and sunglasses when outside for more than one hour on separate 5-point scales, "Never" to "Always," [24] and healthcare provider and self-screening intentions (intend, not intend) as well as basic demographic and skin type information) were assessed.

2.4. Statistical Analysis. To assess message interpretation (aim I), multiple-choice responses are reported descriptively, and via pre-post melanoma perceived risk assessed with a 3 by 2 analyses of covariance (ANCOVA), with vignette type and vignette risk level as the independent variables, controlling for pretest perceived risk. To assess anticipated sun protection behavioral intentions (aim II), hierarchical linear modeling (HLM; [25]) was employed to examine sun protection (intended use of sunscreen, shirts, hats, shade seeking, and sunglasses on separate 5-point scales, "Never" to "Always") given the presumed correlation between outcomes, treating study id as the sole random effect. Statistical evidence was evaluated by the type-III test of Wald statistic, using the MIXED procedure in the SPSS statistical package (v.18). For the dichotomous outcome of skin examination (intend/not intend screening), a generalized estimating equation (GEE; [26]) was used to examine intended skin cancer screening (by healthcare provider as well as skin self-examination). Statistical evidence in the GEE was evaluated by the generalized score tests for type III contrasts using the SAS statistical package (v9.2). The independent variables in the HLM and GEE models were vignette type, vignette risk level, and an interaction between vignette type and risk level. We did not include pretest sun protection behaviors in the HLM, nor pretest skin cancer screening in the GEE models because of sample size limitations [27].

3. Results

Randomization was balanced, as indicated by the lack of significant pretest differences in participants' reported sun protection behaviors and skin cancer screening across participants randomized to different experimental conditions. There were no significant differences across conditions in whether participants reported a sun-sensitive phenotype, whether they had one or more family members with melanoma, nor whether they had a prior personal melanoma history.

3.1. Interpretation of Prototypic Skin Cancer Risk Feedback (Aim I). Positive feedback was interpreted more consistently than negative feedback across all feedback types (see Table 1). Of those who received mutation-positive feedback, two-thirds (67%) interpreted their results to mean that their melanoma risk was increased. Those who received mutation negative findings had more diverse interpretations—only

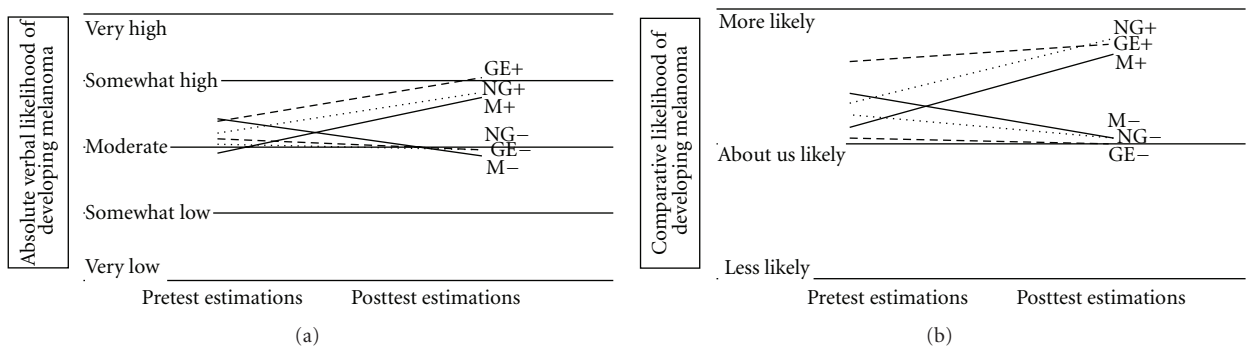

Figure 1: Changes in melanoma risk perceptions (Pretest-posttest). (a) Absolute verbal likelihood. How likely is it that you will develop melanoma in the future? Would you say your chance of getting melanoma is …? (b) Comparative likelihood. Compared to the average person your age, would you say that you are more, less, or about as likely to develop melanoma? GE (gene environment), NG (nongenetic), and M (mutation) are denoted according to feedback, positive or negative (+/–).

one-third (38%) equated their risk to others with a family history of melanoma, yet 33% reported that their risk was decreased, and 25% reported that their risk did not differ from that of the general population. Interpretation of gene-environment risk feedback showed a similar pattern. Most of those who received positive gene-environment feedback (70%) interpreted their results to mean that their melanoma risk was increased, but of those who received negative gene-environment feedback, 30% reported that their risk was decreased, and 30% reported that their risk was similar to the general population. The pattern was similar for those receiving nongenetic feedback as well. Most of those who received positive feedback (70%) interpreted their results to mean that their melanoma risk was increased, but of those who received negative feedback, 41% reported that their risk was decreased, and 32% reported that their risk was similar to the general population. Interestingly, compared to those who received negative gene environment and nongenetic feedback, more who received positive gene environment and nongenetic feedback interpreted their findings to mean that their risk was not different from others with a melanoma family history. Interpretations that melanoma was either ruled out, or inevitable, were almost nonexistent, with the only three participants who reported certainty that they would get melanoma all having received mutation-positive feedback.

To examine the effect of feedback type (mutation, gene environment, nongenetic) and risk level (positive or negative findings) on perceived melanoma risk, two 3 by 2 ANCOVAs (feedback type by risk level, controlling for pretest perceived risk) were used. Main effects for risk level for both verbal absolute risk and comparative risk were found, $F(1, 132) = 59.22$, $P < 0.0001$; $F(1, 132) = 37.37$, $P < 0.0001$, respectively, such that those who received positive findings had significantly heightened anticipated perceived risk for all types of feedback; those who received negative findings had significantly reduced anticipated perceived risk for all types of feedback. There were no significant main effects for feedback type (mutation, gene environment, nongenetic) nor any significant interactions (all $Ps > 0.60$; see Figure 1).

3.2. The Influence of Risk Feedback on Behavioral Intentions (Aim II). Intentions for all sun protection, Wald $F(1, 134.27) = 3703.72$, $P < 0.0001$ and skin cancer screening, GEE: $\chi^2(1, N = 139) = 5.09$, $P = 0.02$, were higher among those receiving positive *versus* negative feedback. Feedback type was not a significant predictor in either the MIXED model ($P = 0.37$) or the GEE ($P = 0.18$), and there were no significant interactions ($P = 0.74$ and $P = 0.30$, resp.). Figure 2 depicts both pretest (self-reported behavior) and posttest (intended changes in behavior) findings. Those who received positive versus negative feedback showed higher levels of intending to maintain consistent (often or always) sunscreen use such that they reported high pretest sunscreen use and high posttest intentions for sunscreen use. For example, 67% who received positive feedback intended to maintain consistent sunscreen *versus* 59% of those who received negative feedback. Positive feedback led to higher intentions to adopt consistent (often or always) shade seeking, such that those who did not report consistent shade seeking at pretest reported that they intended to adopt it at posttest. Those who received positive *versus* negative feedback showed higher levels of intending to maintain healthcare provider screening, as well as increased intentions to adopt skin self-examination. Findings regarding intended use of shirts, hats, and sunglasses are not shown but followed the same pattern.

4. Discussion

This study found that the positive *versus* negative dimension of the prototypic melanoma risk feedback consistently influenced melanoma FDRs' melanoma risk perceptions as well as behavioral intentions. Those study participants receiving positive feedback anticipated higher-risk perceptions compared to pretest levels; those participants receiving negative feedback anticipated lower-risk perceptions compared to pretest levels as evaluated in aim I. Similarly, as evaluated in aim II, anticipated intentions for protective behaviors (such as use of sunscreen and shade-seeking) and screening (provided by a health-care provider, as well as self-screening) increased more among those who received positive risk

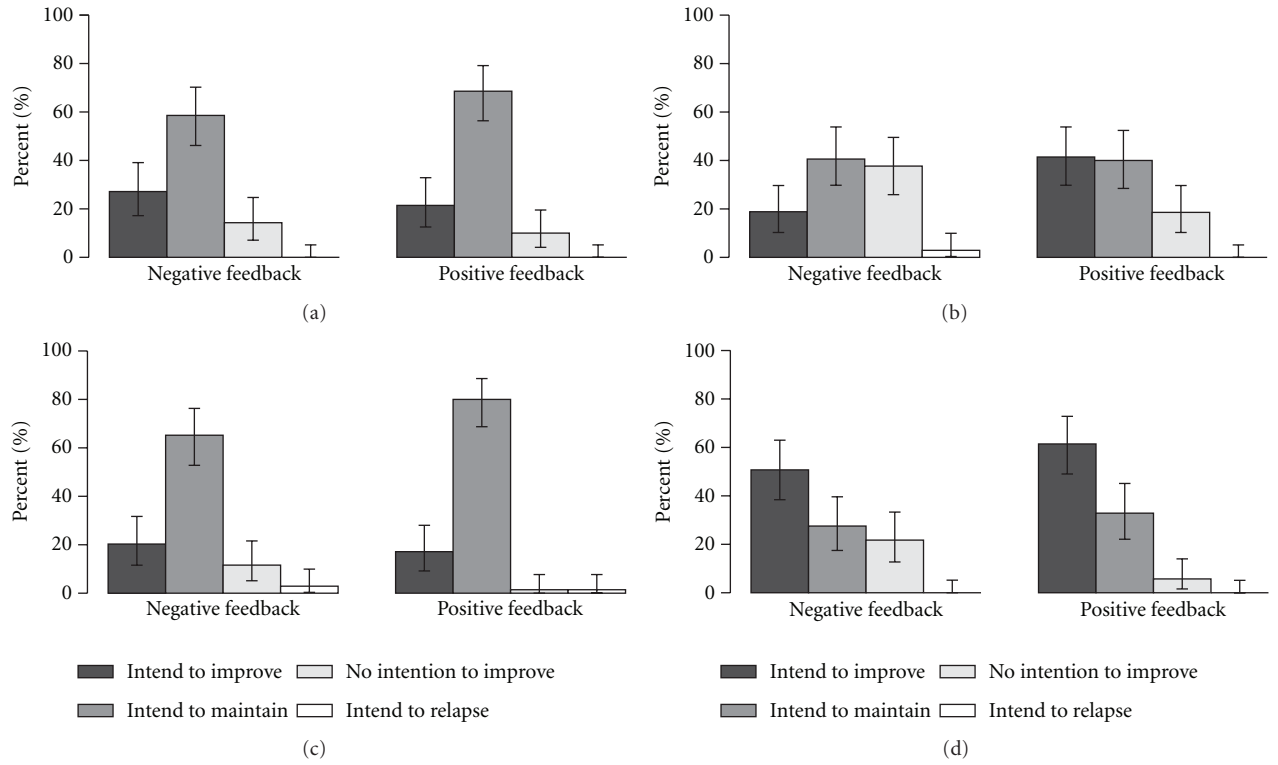

Figure 2: Changes in intentions regarding sun protection and screening (pretest-posttest). (a) Sunscreen use. (b) Shade seeking. For sunscreen use and shade-seeking outcomes, intend to improve is indicated by lower pretest utilization (never, sometimes) and higher posttest intentions (often or always). Intend to maintain is indicated by higher pretest utilization (often or always) and higher posttest intentions (often or always). No intention to improve is indicated by lower pretest utilization (never, sometimes) and lower posttest intentions (never, sometimes). Finally, intend to relapse is indicated by higher pretest utilization (often or always) and lower posttest intentions (never, sometimes). (c) Skin cancer screening by a healthcare professional. (d) Skin cancer self-screening. For screening outcomes, intend to improve is indicated by no reported prior screening at pretest but intentions to screen at posttest. Intend to maintain is indicated by reported prior screening at pretest and intentions to screen at posttest. No intention to improve is indicated by no reported prior screening at pretest and no intentions to screen at posttest. Intend to relapse are indicated by reported prior screening at pretest, yet no intentions to screen at posttest.

feedback, confirming the theoretical connection between increased risk judgments and intentions to self-protect [28]. Recent studies have documented that individuals at moderate cancer risk are not highly sensitive to low-penetrance genetic quantitative risk magnitude and pictorial information [29–31] and that findings regarding whether a test was "positive" or "negative" may be more salient than the exact percentage risk feedback [11]. Indeed, genetic risk feedback necessarily contains two dimensions: first, whether a genetic mutation or risk variant is identified or not; second, what quantitative risk level the genetic mutation or variant confers. This may be because the easily understood "gist" is the presence or absence of the risk-conferring gene mutation or variant. It may be that the risk level is only salient to those who have already been identified to have a risk-conferring genetic factor present. For those receiving negative feedback, or feedback that a risk-conferring genetic factor is not present, it may be most important for them to integrate their findings with other relevant personal risk information.

We found that negative feedback led to more varied interpretations than positive feedback, with over half of those receiving negative feedback interpreting their feedback as either decreased melanoma risk, or as risk similar to the general population. It is possible that some of those receiving negative feedback may have discounted their family history—despite the clarity with which this information was presented—either defensively [14], or because of a recency effect [32] since hypothetical genetic feedback findings were presented subsequent to the family history risk statement. This is of potential concern given that early adopters of genetic testing outside the high-risk clinic are likely to include those with family disease histories who may be more motivated to use their genetic test findings to minimize their concerns than to amplify them. Some who received positive feedback did not interpret their risk to exceed that of others with a melanoma family history, as this was a more common interpretation among those who received positive (versus negative) gene environment or nongenetic feedback. Suggestions for careful presentation of negative findings include prominent repetition of reminders about other relevant risk factors, including family history, after genetic test findings are conveyed, as well as consideration of whether different types of risk information can and should be integrated in genetic risk calculations. Most importantly, we

advocate for the careful evaluation of message interpretation and comprehension prior to the use of these messages in direct-to-consumer contexts.

An analog study presents both opportunities and limitations. The use of scenarios is a widely used research strategy to examine decision-making processes associated with genetic testing [22]. It is possible that the brevity of prototypic feedback may have impeded interpretations of negative findings, in particular. Another limitation involved the fact that 14% of our FDR participants also had a personal melanoma history, which was an additional source of risk heterogeneity in our sample. However, our results clearly showed that those who received positive feedback both increased their risk perceptions and showed higher intentions for behavior change, supporting relatively accurate interpretations of the positive *versus* negative feedback dimension. A strength of our study involved the use of first-degree family members of melanoma patients who are at actual increased melanoma risk based on their family history [33], as well as the fact that changes in risk judgments led to changes in intended behavior change predicted by major health behavior theories [28]. Our findings need to be confirmed in actual testing situations, with larger samples that will allow stratification across skin type, sun exposure histories, strength of family history, and whether individuals have a personal melanoma history, with longitudinal followup of actual sun protection and skin cancer screening adoption.

In conclusion, much remains to be learned regarding the translational behavioral potential of human genomics, especially outside of the high-risk setting where extensive genetic counseling will be unavailable or not required. Our study casts a spotlight on the need to conduct further research on those who receive negative genetic feedback, who may be relieved about their findings and yet discount other important cancer risk factors.

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Research Article

Do Breast Cancer Patients Tested in the Oncology Care Setting Share *BRCA* Mutation Results with Family Members and Health Care Providers?

Susan T. Vadaparampil,[1,2] Teri Malo,[1] Cara de la Cruz,[1] and Juliette Christie[1]

[1] *Health Outcomes and Behavior Program, Division of Cancer Prevention and Control, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA*
[2] *Department of Oncologic Science, College of Medicine, University of South Florida, 12901 Bruce B. Downs Boulevard, Tampa, FL 33612, USA*

Correspondence should be addressed to Susan T. Vadaparampil, susan.vadaparampil@moffitt.org

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BRCA genetic test results provide important information to manage cancer risk for patients and their families. Little is known on the communication of genetic test results by mutation status with family members and physicians in the oncology care setting. As part of a longitudinal study evaluating the impact of genetic counseling and testing among recently diagnosed breast cancer patients, we collected patients' self-reported patterns of disclosure. Descriptive statistics characterized the sample and determined the prevalence of disclosure of *BRCA* test results to family members and physicians. Of 100 patients who completed the baseline and the 6-month followup survey, 77 reported pursuing testing. The majority shared test results with female first-degree relatives; fewer did with males. Participants were more likely to share results with oncologists compared to surgeons, primary care physicians, or other specialty physicians. These findings suggest that while breast cancer patients may communicate results to at-risk female family members and their medical oncologist, they may need education and support to facilitate communication to other first-degree relatives and providers.

1. Introduction

Mutations in the *BRCA1* and *BRCA2 (BRCA)* genes place individuals at higher risk of developing breast and ovarian cancer, compared to those without a mutation [1, 2]. A recent study of cancer risks in *BRCA* mutation carriers in a large US-based sample estimated the cumulative breast cancer risk at age 70 years to be 46% in *BRCA1* carriers and 43% in *BRCA2* carriers. Cumulative ovarian cancer risk was 39% in *BRCA1* carriers and 22% in *BRCA2* carriers [3]. Although less well-established, elevated cancer risks in men from *BRCA* families have been reported in male breast cancer (6–8%) [4–10] and prostate cancer (20–30%) [5, 8, 10–27]. Individuals who undergo genetic testing and discover that they carry a *BRCA* mutation can manage their cancer risk through intensive screening, prophylactic surgery, and/or chemoprevention [28–31]. Criteria set forth by the National Comprehensive Cancer Network to identify and refer breast cancer patients to a genetics professional [32] include a personal history of early onset breast cancer (i.e., diagnosed $\leq$ age 50), triple negative breast cancer, and/or ≥ 2 primary cancers. Women diagnosed with breast cancer at any age may also be referred when there is a family history of early onset breast cancer, ovarian cancer at any age, and/or male breast cancer. Additionally, women with a family history of breast cancer and cancers considered to be part of the Hereditary Breast Ovarian Cancer spectrum (e.g., pancreatic, thyroid) may also warrant genetic evaluation.

Clinical guidelines indicate the most informative clinical testing strategy is to first test a family member with cancer [33]. Then, if a familial mutation is identified, testing can be offered to unaffected family members to determine whether they have the already identified *BRCA* mutation [33]. If there

was a previously identified mutation in the family and the proband's test way negative (i.e., true negative), the proband generally is considered to be at general population risk for cancer. In this situation, there is a high level of reassurance that *BRCA* mutations are not the underlying cause of cancer, which may reduce anxiety as well as unnecessary screening and surveillance in the proband and at-risk family members. Conversely, test results are considered uninformative if an individual is the first person in the family to have testing and receives a negative result or if an alteration in the *BRCA* genes is detected but the clinical significance for the alteration is unknown (i.e., variant of uncertain significance). In this situation, cancer risk is determined based on personal and family cancer history.

In order for genetic test results to maximally benefit and impact clinical management, test results must be communicated to others. To impact the health of family members, probands must share results with at-risk relatives [34]. For management of the proband's personal cancer risk, healthcare providers must also be aware of test results. The healthcare system's emphasis on patient confidentiality, clinical practices in which genetic testing results may not be included as part of the "main" medical record, and position statements from professional organizations such as the American Society of Clinical Oncology [35] and the American Society of Human Genetics [36] indicating that providers generally do not share genetic testing information and results with family members who are not their patients may limit the ability of providers to participate in dissemination of test results among family members. As such, the responsibility of communicating *BRCA* test results likely falls on the probands themselves. Prior studies of communication of test results to family members have found that the majority of participants share test results with family members, typically within the first few months of receiving test results. However, frequency of disclosure may vary based on test result as well as the family members' age, gender, and degree of relatedness (e.g., first-degree versus second-degree relative) [37–48]. Qualitative and quantitative studies also demonstrate that probands sometimes express difficulty in sharing results with at-risk relatives, particularly when relationships are emotionally distant or test results are uninformative [43, 44, 49].

An understudied aspect of communication regarding *BRCA* test results is whether results are shared with individuals outside of the family structure, namely, health care providers. Given that probands are often identified due to a personal cancer diagnosis and subsequently receive counseling and testing in the oncology care setting, it is important that as they transition into survivorship and shift health care back into the community setting, primary care providers are also made aware of *BRCA* test results [50, 51]. Despite the important role that health care providers play in providing care to patients based on *BRCA* test results, only two studies have examined communication of *BRCA* test results to health care providers. In a study of 69 patients referred to a cancer risk assessment program, the majority of patients shared results with both oncology (64–88%) and primary care providers (74–81%) [50]. In a larger study of 312 patients who underwent *BRCA* testing at a large comprehensive cancer center, most (72%) shared genetic test results with health care providers outside of the oncology care setting [51].

Some data suggest patients affected with cancer may react differently than unaffected probands to the cancer genetic counseling and testing process [52–54] including communication of test results [40, 51, 55]. It is possible that having genetic counseling and testing following a cancer diagnosis may delay or reduce the likelihood that patients disseminate test results to at-risk family members due to both the physical and emotional stressors of diagnosis and treatment. Despite the arguable equal importance of affected probands sharing test results with both at-risk family members and health care providers, to our knowledge, no prior study has examined disclosure patterns to family members and physicians in a group of affected patients in a single study. To that end, the primary focus of our paper is to describe the frequency of communication of test results among breast cancer patients who have undergone genetic counseling and testing in the breast oncology care setting. The findings from this study will inform the development of comprehensive interventions that facilitate communication of test results by probands to both family members and health care providers.

2. Method

2.1. Participant Recruitment. This substudy regarding communication of *BRCA* test results is part of a larger longitudinal investigation of the impact of genetic counseling on psychosocial and behavioral outcomes among breast cancer patients referred for genetic counseling in the oncology care setting. Eligibility criteria for the larger study included: (a) meeting National Comprehensive Cancer Network cancer genetics referral criteria [32], (b) $\geq$18 years of age; (c) confirmed personal breast cancer diagnosis based on medical records review; (d) no previous participation in genetic counseling (GC) and/or testing for hereditary breast and ovarian cancer (HBOC); (e) capable of speaking and reading standard English; (f) having a mailing address and working telephone number; and (g) having a GC appointment scheduled at Moffitt Cancer Center.

Upon Institutional Review Board approval, recruitment took place between April 2009 and July 2010 with followup completed in February 2011. Data were collected: (a) after scheduling but prior to the pretest genetic counseling appointment (T1), (b) within two to three weeks after participants completed pretest genetic counseling (T2), and (c) six months after completing genetic testing (T3). The current report is focused on the communication of *BRCA* mutation test results; therefore, analyses are based on T1 (sociodemographic and clinical) and T3 (communication of test results) data.

All patients in the current study received in-person pretest GC by a Masters-level prepared genetic counselor through the clinical GC and testing service at the Cancer Center. For those who proceeded with testing, the majority received testing by the sole clinical laboratory for *BRCA*

testing in the US. Those who were uninsured or unable to obtain insurance coverage for testing were informed of a research study at another institution where they were able to receive *BRCA* testing free of charge. Those who proceeded with testing were subsequently scheduled for either an in-person or telephone-based posttest results disclosure session. Those patients then received followup letters summarizing their pre- and posttest GC sessions.

The study team reviewed the GC appointment schedule weekly for women meeting study eligibility criteria. Eligible patients were mailed an introductory letter with a toll-free number to opt out of further contact by the study team, the T1 survey, two consent forms, and a preaddressed envelope. Approximately one week from the mailing date, patients who did not opt out were contacted via telephone to confirm receipt of study materials and to answer any questions about the study. For those not reachable by telephone prior to their scheduled GC appointment, the study coordinator met briefly with patients after their GC session to determine whether the T1 survey was complete. Those who did not complete the T1 survey before attending their pretest GC session were considered decliners.

For the first six weeks of study recruitment, patients who failed to attend their pretest GC appointment were considered ineligible. However, this strategy precluded the opportunity to include patients who rescheduled and attended their GC appointment. Thus, recruitment procedures were revised so that patients who scheduled a new appointment were mailed an additional introductory study packet. Patients who failed to reschedule their appointment between the date of their canceled appointment and July 2010 (end of recruitment period) were considered ineligible. Participants received a $25.00, $20.00, and $30.00 gift card for completing T1, T2, and T3, respectively. Those patients who completed the T1 and T3 assessments and reported *BRCA* genetic test results were included in the current analyses.

3. Measures

Sociodemographic and clinical characteristics obtained from patient questionnaires or medical records review included: current age, age at diagnosis, time since diagnosis, current stage of breast cancer (1, 2/3, 4, unstaged, other [e.g., unknown]), previous surgery (yes, no), and primary payor at diagnosis (private insurance, public insurance, no insurance, other). In addition, we classified *BRCA* mutation status as: positive, true negative (i.e., tested negative for known familial *BRCA* mutation), and uninformative (tested negative in the absence of a known familial *BRCA* mutation or had an indeterminate or variant of uncertain significance result). We excluded 15 people who indicated they either did not know or had an "other" test result from the analyses examining disclosure of test results to family members and physicians. Additional data collected via self-report questionnaires included: education (completed high school or less; vocational school and some college; college graduate and beyond), total household income at time of diagnosis (≤35,000; >35–≤50,000; >50,000), marital status (married/living with partner, other), and race (Black, White, other).

Family communication of *BRCA* test results was assessed using an abbreviated version of the Family Communication Measure, developed by Patenaude and colleagues [43]. Respondents were asked to complete the following information for each first-degree relative : relative still living (yes, no), age, and status of result disclosure (shared, did not share).

Communication of results to health care providers was assessed with a single item developed for the current study where participants were first asked whether they shared their results with a health care provider (yes, no, do not know). Those who responded "yes" were asked to select the specialties for each of the providers with whom they shared the information (surgeon, oncologist, obstetrician/gynecologist [OBGYN], primary care doctor, doctor of another specialty, or other health care provider).

3.1. Data Analysis. Descriptive statistics were calculated to characterize the sample and to determine the prevalence of disclosure of *BRCA* test results to family members and physicians. To determine the prevalence of *BRCA*-test result disclosure, the proportions of living relatives with whom test results were shared stratified by family member (e.g., mother) and participant *BRCA* status (positive, true negative, uninformative) were calculated. Statistical analyses were conducted using SAS (Version 9.2, Cary, NC).

4. Results

As shown in Figure 1, a total of 223 patients were identified by the genetic counselor as potential participants who had scheduled an appointment for GC. Of these, 87 patients did not meet eligibility requirements (e.g., previous participation in GC and/or testing for HBOC, rescheduled GC appointment more than three times, nonEnglish speaking). Of the remaining 136 eligible participants, 114 consented and completed the T1 survey, resulting in an 83.8% response rate. Of those 114, 100 completed the T3 assessment that included questions about communication of test results. Data analyses were conducted on 77 women who reported pursuing *BRCA* testing.

As detailed in Table 1, study participants were on average 48 years old at the time of diagnosis. At the time of the T1 survey, participants were on average 52 years old and a median of 9.7 months had passed since they were diagnosed. The majority was married or living with a partner (66.2%); white (81.8%); at least a college graduate (46.8%); and covered by private insurance (57.1%). The greatest proportion had an annual household income of more than $50,000 at the time of diagnosis (39.0%). Regarding clinical variables, the greatest proportion of participants (31.2%) were in stage 2 or 3 and the vast majority (83.1%) had previous surgery for their breast cancer. In terms of *BRCA* test result, 40.3% had a true negative result, 3.9% tested positive, and 14.3% had an uninformative result.

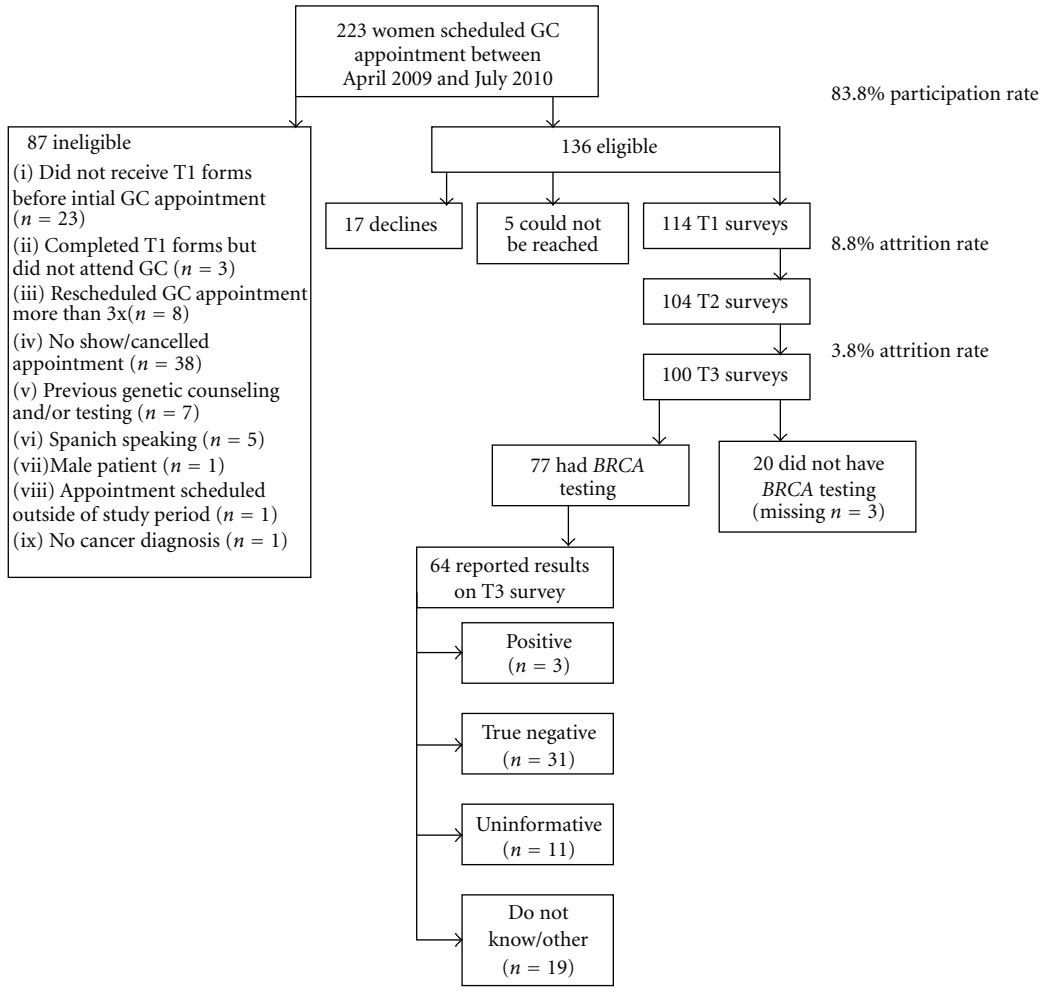

Figure 1: Study flow diagram.

As seen in Table 2, most probands communicated results with family members, regardless of the test results. Of participants who tested positive ($n = 3$), all shared their test results with their mothers, fathers, and sisters, whereas participants shared with half of daughters aged 18 or older and brothers, on average. Of those who tested true negative ($n = 31$), sharing of results with first-degree relatives ranged from an average of only 67% of daughters younger than age 18 up to 100% of sons younger than 18. Participants with uninformative results ($n = 11$) shared results with all sons or daughters age 18 years or older. In general, a greater proportion of participants reported sharing their test result with all female relatives compared to male relatives. Participants who tested true negative reported sharing results with an average of 90–100% of female relatives aged 18 or older compared to 83–89% of male relatives. Those with an uninformative result shared with an average of 80–100% of female adult relatives compared to 56–100% of male adult relatives. Regarding disclosure to minor children (age 18 years or younger), those who tested true negative shared their result with an average of 67% of minor daughters and 100% of minor sons. Those with an uninformative test result shared with half of minor daughters and none of minor sons. Figure 2 summarizes patients' reports of communication of genetic test results with health care providers. Overall, 74% shared their test results with their oncologist and 51% with their surgeon. They were less likely to share results with their primary care physicians (40% of OBGYNs and 49% of primary care physicians) or other specialty physicians (9%).

5. Discussion

Overall, our study suggests that frequency of disclosure of genetic test results by probands varies by mutation status, gender of at-risk relatives, and age of at-risk relatives. For health care providers, disclosure rates varied by specialty.

Although based on a limited sample size, our findings suggest variability in disclosure patterns based on mutation status. Women who tested positive were most likely to communicate results to both parents and all sisters (100%), compared to those who tested true negative or uninformative. It is possible that the differences between positives and true negatives may be due to the fact that women who were in the true negative category were being tested for a previously

Table 1: Sociodemographic and clinical characteristics of study participants who had *BRCA* testing ($n = 77$)[a].

Characteristic	Mean (SD, range)
Age at diagnosis (years)	47.6 (10.7, 24–69)
Current age (years)	52.0 (10.9, 25–70)
Time since diagnosis (months)	44.5 (70.2, 0.6–339.9)
	n (%)
Current stage	
Stage 1	19 (24.7)
Stage 2/3	24 (31.2)
Stage 4	6 (7.8)
Unstaged	7 (9.1)
Other/unknown	14 (18.2)
BRCA test result	
Positive	3 (3.9)
True negative	31 (40.3)
Uninformative	11 (14.3)
Do not know/other	19 (24.7)
Did not report result	13 (16.9)
Previous surgery	
Yes	64 (83.1)
No	9 (11.7)
Primary payor at diagnosis	
Private insurance	44 (57.1)
Public insurance	18 (23.4)
No insurance	2 (2.6)
Other	11 (14.3)
Education	
High school or less	13 (16.9)
Vocational school/some college	25 (32.5)
College graduate and beyond	36 (46.8)
Total household income prior to diagnosis	
≤35 K	20 (26.0)
>35 K to ≤50 K	12 (15.6)
>50 K	30 (39.0)
Prefer not to answer	14 (18.2)
Marital status	
Married or living with partner	51 (66.2)
Other	26 (33.8)
Race	
White	63 (81.8)
Black	5 (6.5)
Other	6 (7.8)

[a] Percentages may not add up to 100 due to missing data.

identified mutation in the family. Thus, some parents and sisters may have already been tested, making it less likely that patients would see the need to disclose test results to other relatives who already have definitive information about their mutation status. This explanation is supported by the observation that those who were true negative were more likely to share results with brothers and children (i.e., those not likely to have had prior testing) when compared to those

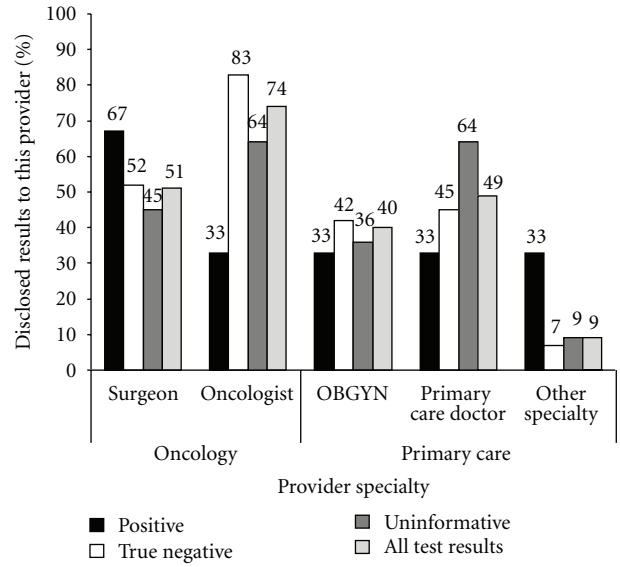

Figure 2: Patients' report of sharing test results by provider specialty and mutation status.

who tested positive. It is also possible that those who test negative for a known familial mutation may feel a sense of guilt in sharing results with relatives who are positive (most likely parents or sisters who have been tested) [56, 57].

Similar to prior studies [43], those who received uninformative results were also less likely to share results with family members compared to those who tested positive. Women with these test results may have difficulty understanding and communicating test results to family members due to both cognitive and emotional factors. A few studies of women who received uninformative test results suggest that they are likely to express uncertainty, misinterpret their test results [58, 59], or report negative emotional reactions such as anger and frustration [59]. Communication of uninformative test results may occur less often because of probands'concern that at-risk relatives would take the results to mean they were not at increased risk for breast cancer [42]. This is evidenced by a recent study of 39 relatives of probands who received uninformative test results; relatives' medical decisions were based on their own perceptions of increased cancer risk and generally did not correlate with information actually communicated to them by the proband [34].

As observed in prior studies [43, 45, 46, 48, 55], probands were more likely to disclose test results to female relatives in each test result category. This finding is likely due to the higher cancer risks and greater availability of prevention/risk management options for female patients. However, given the equal risks of transmitting *BRCA* mutations to male and female offspring, increasing documentation of male cancer risks [60], and emerging surveillance guidelines for male *BRCA* mutation carriers [61], it is critical that female patients understand the importance of sharing test results with all at-risk relatives.

Another interesting observation from our study that is consistent with recent investigations on this topic is the

Table 2: Frequency of sharing test results with first-degree relatives by mutation status.

Relationship		Shared results *n* (%)		
		Positive ($n = 3$) *n* or % (range)	True negative ($n = 31$) *n* or % (range)	Uninformative ($n = 11$) *n* or % (range)
Parent	Mother ($n = 16$)	$n = 1$	$n = 10$	$n = 5$
	n (%)	1 (100.0)	9 (90.0)	4 (80.0)
	Father ($n = 19$)	$n = 1$	$n = 12$	$n = 6$
	n (%)	1 (100.0)	10 (83.3)	4 (66.7)
Sibling	Sister ($n = 23$)	$n = 2$	$n = 14$	$n = 7$
	Avg. number per participant	1.5 (1.0–2.0)	1.6 (1.0–4.0)	2.1 (1.0–4.0)
	Avg. % disclosed	100.0 (100.0-100.0)	92.9 (0.0–100.0)	91.7 (66.7–100.0)
	Brother ($n = 22$)	$n = 2$	$n = 16$	$n = 4$
	Avg. number per participant	2.0 (1.0–3.0)	1.6 (1.0–4.0)	2.0 (1.0–4.0)
	Avg. % disclosed	50.0 (0.0–100.0)	89.1 (0.0–100.0)	56.3 (0.0–100.0)
Child	Daughter			
	<18 years ($n = 4$)	$n = 0$	$n = 3$	$n = 1$
	Avg. number per participant	—	1.3 (1.0–2.0)	2.0 (—)
	Avg. % disclosed	—	66.7 (0.0–100.0)	50.0 (—)
	18+ years ($n = 19$)	$n = 2$	$n = 12$	$n = 5$
	Avg. number per participant	1.5 (1.0–2.0)	1.3 (1.0–2.0)	1.4 (1.0–2.0)
	Avg. % disclosed	50.0 (0.0–100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
	Son			
	<18 years ($n = 7$)	$n = 0$	$n = 5$	$n = 2$
	Avg. number per participant	—	1.0 (1.0-1.0)	2.0 (2.0-2.0)
	Avg. % disclosed	—	100.0 (100.0-100.0)	0.0 (0.0-0.0)
	18+ years ($n = 15$)	$n = 0$	$n = 9$	$n = 6$
	Avg. number per participant	—	1.4 (1.0–3.0)	1.7 (1.0–3.0)
	Avg. % disclosed	—	83.3 (0.0–100.0)	100.0 (100.0-100.0)

*Excluded those who did not share their results.
*Analyses are based on living relatives and include participants who reported at least one living relative in each relationship category.

disclosure of test results to minor children. While there are specific recommendations against *BRCA* testing for minors [35, 62], there are less clear guidelines regarding disclosure of parents' test results to children. Because there are no recommended surveillance or risk reduction options prior to age 25 for known *BRCA* mutation carriers, there has been debate about the possible negative sequelae associated with disclosing cancer risk to minor children. Yet, several studies have documented that parents share test results with their minor offspring [37, 38, 63–65]. In our study, of the three women with positive *BRCA* test results, none had a daughter or son below the age of 18. Those who tested true negative shared results with an average of 67% of minor daughters and shared uninformative test results with at least one daughter. The largest published study to date on this topic included 253 parents who had undergone *BRCA* testing and 505 offspring. Not surprisingly, for those who shared true negative results, children often expressed relief. However, parents perceived distress more frequently among offspring learning about their parent's *BRCA* positive or variant of uncertain significance result [38]. Thus, consideration of developmentally appropriate psychosocial interventions to support children who learn of *BRCA* mutation status, particularly positive and uninformative results, is warranted.

With regard to sharing results with health care providers, it appears that women were more likely to share results with oncology care providers, particularly medical oncologists. Prior studies document that fewer women attend GC (and therefore pursue testing) prior to surgical treatment for breast cancer [66, 67]. Thus, the sharing of results with medical oncologists likely reflects the greater proportion of women referred by medical oncologists who generally assume their care after surgery. This finding is also supported by several studies of provider utilization of GC and testing that suggest when compared to other oncology care physicians (e.g., surgeons, radiation oncologists), medical oncologists have higher levels of knowledge and utilization of *BRCA* testing [68–70]. It is possible that the rates of sharing results with providers in the oncology care setting may also reflect probands' assumptions that all providers from a single institution would be made aware of or have access to genetic test results. However, at some institutions, *BRCA* results may be kept out of the "main" medical record and not accessible to all physicians involved in a patient's

oncology care [71]. The health professional providing pre- and posttest GC should also discuss the patient's preferences for informing the relevant oncology providers based on specific institutional policies about documentation of *BRCA* test results.

Overall, participants reported sharing test results less often with primary care providers compared to oncology care providers. The frequency of sharing results (40–49%) is similar to another study that examined sharing of *BRCA* genetic test results with nononcology health care providers (30–44%) [51]. It is noteworthy that although patients in our study were only ~5 months from receiving test results, compared to the other study where participants may have been several years from testing (as early as 1997), rates of test result disclosure were similar for both populations; this suggests low rates of disclosure with primary care providers may persist over time. As time elapses, most breast cancer patients tested in the oncology care setting will transition into survivorship and their care will move back into the primary care setting [72]. Primary care physicians will assume more responsibility for prevention or risk management of secondary cancers in these patients. Thus, it is important to encourage breast cancer patients to share results with their primary care providers.

While our study presents important information about the frequency with which genetic information is shared with at-risk relatives and health care providers, findings should be considered in light of certain limitations. First, our sample size is small and did not allow for statistical analyses of differences in disclosure based on variables such as mutation status, gender of relative, or provider type. However, ours is the first study to focus on this issue exclusively among affected breast cancer patients and provides preliminary data to support larger studies focused on understanding and supporting disclosure of *BRCA* test results among patients receiving counseling and testing at or near the time of a breast cancer diagnosis. Second, we evaluated sharing of test results during a relatively short time period (~5 months post receipt of *BRCA* test results). However, prior studies suggest that the majority of test result disclosures with first-degree relatives occurs within weeks to a few months of when the proband receives their test results [43, 47]. Similarly, we observed consistent rates of communication with health care providers between our study and one that included breast cancer survivors who were several years from the time of testing [51]. This implies that if communication does not occur early, it will not likely occur later. Third, we did not assess detailed communication beyond first-degree relatives. However, given that first-degree relatives are at highest risk for inheriting a *BRCA* mutation and most likely to be informed by a proband's test results, we selected to focus on this group to minimize participant burden of a lengthy questionnaire that would be required to assess additional at-risk relatives. Our sample for the present study represents a subset of women from a larger study who remained in the study for the six-month assessment and were also willing to share test results. In this sense, selection bias should be considered when interpreting out results; it is possible that our results do not capture the full variability of disclosure patterns among women in this population. Finally, we did not directly assess whether patients had a previously identified *BRCA* mutation in the family. Patients who were undergoing testing for a known family mutation may not need to communicate results with other at-risk relatives given this information may have already been provided by the initial relative who tested positive.

6. Conclusion

Communication of *BRCA* test results is a critical step toward realizing the benefit of genetic technology to identify cancer risk both for individuals and family members. In light of current ethical and legal concerns regarding privacy of patient genetic information [71, 73], probands are often responsible for sharing test results both to at-risk relatives and health care providers. Prior research suggests that, to a large extent, they are willing to accept and carry out that responsibility [74]. However, our study demonstrates key areas where breast cancer patients who choose to undergo GC and genetic testing may need further education and support to facilitate accurate and effective communication to inform at-risk family members' medical decisions and care while minimizing psychosocial burden and familial distress.

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