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ORIGINAL ARTICLE

Prevalence of mutations in a diverse cohort of 3162 women tested via the same multigene cancer panel in a managed care health plan

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Abstract

Advances in gene sequencing of mutations related to hereditary cancers have enabled expansion of this testing to patients cared for in community clinics. Our goal was to report on the prevalence of pathogenic/likely pathogenic variants (PV/LPV) and the distribution of mutations by cancer history in a diverse cohort. We evaluated 3162 women in a large non-profit health plan who were referred for cancer genetic counseling and tested them via the same multigene cancer panel. We examined the pathogenic variant/likely pathogenic variant (PV/LPV) prevalence for 20 genes by clinical factors, demographics, and personal or family cancer history. We calculated adjusted odds ratios for the association between race/ethnicity and mutation results. The majority of women (65.4%) were referred post-breast or ovarian cancer diagnosis. The overall prevalence of any PV/LPV result was 11.7%. Overall, nearly 5.4% had *BRCA*1/2 mutations, while 6.3% had at least one mutation in non-*BRCA* genes. In the subset with any PV/LPV result, 55.0% of the total mutations were in non-*BRCA* genes. The distribution of mutations was similar in those with or without a personal cancer history. Latina women were somewhat less likely to have mutations in non-*BRCA* genes implicated with breast cancer (OR = 0.55, 95% CI 0.36–0.87). Given that 55.0% of the PV/LPV results were in genes other than *BRCA*1/2, regardless personal or family cancer history, the study suggests that multigene cancer panel testing may be appropriate for detecting germline mutations in a high-risk cohort in a managed care or public health setting.

Keywords *BRCA* · Cancer gene panel testing · Breast cancer · Mutations · Population based

Introduction

Since the discovery that mutations in *BRCA* genes lead to hereditary breast and ovarian cancer syndrome (Hall et al. 1990), aberrations in several genes have been linked to inherited predisposition to cancers in various organ systems. The identification of pathogenic mutations in both *BRCA* and non-*BRCA* genes can provide clinical benefit to individuals, including risk-adapted prevention strategies and targeted therapeutic methods (Kurian et al. 2014). Multigene cancer panel tests for women at risk for hereditary breast and ovarian cancer were introduced in 2012, but limited information exists about the use of such tests among patients cared for in community health centers. Next-generation sequencing (NGS) has been used for cancer diagnostics in academic settings; however, little is known about its use in community hospitals and the characteristics of those patients who are referred, counseled, and tested (Kurian et al. 2014). Further, prior studies were based on mainly Caucasian populations, included data from different genetics and non-genetic providers, included data from patients who underwent panel testing with different genes, or did not have direct access to the patients' pre- and post- test medical record to track health history over time (Desmond et al. 2015; Easton et al. 2015; Kapoor et al. 2015; Mauer et al. 2014; Norquist and Swisher 2015; Yorczyk et al. 2015; Ricker et al. 2016). Hence, our goals were as follows: (1) to examine the prevalence of pathogenic/likely pathogenic variants (PV/LPV results) and the distribution of mutations in a large cohort of health plan members who had comprehensive genetic counseling mainly for hereditary breast or ovarian cancer, and who underwent the same cancer gene panel testing and (2) to determine if these results varied by personal or family history and race/ethnicity.

Using an evidence-based approach, the custom-designed high/moderate risk cancer gene panel included 20 actionable

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cancer susceptibility genes gleaned from the literature based on clinical validity and utility: *APC, ATM, BMPR1A, BRCA1, BRCA2, CDH1, CDKN2, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, PTEN, SMAD4, STK11, TP53,* and *VHL*.

Methods

Setting, design and subjects

Study participants for this cross-sectional study were drawn from Kaiser Permanente Southern California (KPSC), an integrated non-profit healthcare delivery system with over 4.5 million members, 14 medical centers, and a network of 6200 physicians. Since 2014, KPSC implemented inherited cancer susceptibility testing via a high/moderate risk cancer gene panel for selected patients with clinical presentations or family histories that suggested more than one cancer syndrome. The KPSC healthcare system follows guidelines of the U.S. National Comprehensive Cancer Network (NCCN) for referrals for genetic counseling and testing for hereditary breast, ovarian, pancreatic, and colorectal cancers (NCCN 2019). Briefly, clinicians at each of the 14 KPSC medical centers throughout southern California can refer their patients to a genetic counselor; patients diagnosed with cancer at early ages (< 60 years) and/or have a family history suggestive of a single inherited cancer syndrome are referred for genetic counseling and testing.

A total of 3481 women (age ≥ 18 years) were referred for genetic counseling and cancer gene panel testing between July 2014 and May 2016, and after excluding patients who previously received negative test results before the panel test (either single gene test or specific syndrome test, $N = 313$) and six patients with unclear results, 3162 women remained for analysis. We used the health plan's Surveillance, Epidemiology, and End Results (SEER)–affiliated cancer registry to obtain personal cancer diagnosis information and tumor characteristics (age at diagnosis, anatomic site, histology, and stage at diagnosis). Cancer histories (personal and/or family) were identified using a combination of the health plan's cancer registry and/or medical record review of genetic counseling clinical notes. Demographics including age at the test date, race/ethnicity, and educational level, body mass index (BMI), and comorbidities were captured by linkage to the electronic health record (EHR). In a subset of subjects with PV/LPV results, we performed medical record review to assess personal and family history, an important covariate. The study was approved by the KPSC Internal Review Board.

Cancer gene panel test

Patients had their peripheral blood drawn at KPSC, and samples were shipped to GeneDx, a commercial laboratory. The cancer gene panel tests were performed using next-generation sequencing (NGS) as well as exon-level array comparative genomic hybridization or multiplex ligation-dependent probe amplification for deletion/duplication testing. Results were categorized as positive for a pathogenic or likely pathogenic variant (PV/LPV), variant of unknown significance (VUS), or negative (no variant detected). We categorized the 20 genes into four main groups according to diseases/syndromes implicated with them: (1) *BRCA* genes (*BRCA1, BRCA2*), (2) other breast cancer susceptibility genes (*ATM, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*), (3) Lynch syndrome (non-polyposis colon cancer) genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and (4) other panel genes (*APC, BMPR1A, CDKN2A, MUTYH, SMAD4, VHL*).

Patient characteristics and statistical analysis

The PV/LPV prevalences were compared by demographic characteristics, personal and family history of cancer, and cancer anatomic sites. Mutation (PV/LPV) prevalences for each individual gene were also calculated. Distribution of mutations by the four major groups of genes was compared graphically by personal and/or family cancer history. Multivariable logistic regression models were used to calculate odds ratios and 95% confidence intervals adjusting for age at testing, history of cancer, and race/ethnicity to assess the association between the patient characteristics and mutation status.

Results

Demographics

A total of 3162 women underwent first-tier cancer gene panel testing between July 2014 and May 2016. Demographic characteristics by mutation status are displayed in Table 1. The median age at testing for these women was 51 years. The distribution of race/ethnicity was as follows: Western/Northern European (42.0%), Latina/Hispanic (32.2%), Asian (13.3%), African-American (10.2%), Ashkenazi Jewish (4.1%), and Native American (5.1%). Nearly 22.5% of women had only a family history of cancer, 7.4% had personal history only, and 70.1% had both personal and family history. Interestingly, use of genetic testing was correlated with higher geocoded education; women who underwent genetic testing lived in areas where more than three quarters of residents completed high school or some college. For example, use of genetic testing was the greatest in the areas with the highest geocoded education (74.4%) versus with the lowest (6.4%) or middle (19.2%). Nearly 44.8% had no other comorbid conditions (other than a prior cancer diagnosis) as demonstrated by the Charlson comorbidity index.

Table 1 Mutation (PV/LVP) prevalence by demographic characteristics

	Pathogenic/likely pathogenic variant		Total		PV/LPV prevalence
Total	371	371,100.00	3162	100.00	11.73
Age at testing					
< 40	80	21.56	624	19.73	12.82
40–49	106	28.57	943	29.82	11.24
50–59	100	26.95	762	24.10	13.12
60+	85	22.91	833	26.34	10.20
Mean (SD)	49.8 (12.6)		50.6 (12.9)		
Median (range)	49 (20, 87)		50 (15, 92)		
History of cancer					
Family hx of cancer	63	17.00	713	22.55	8.83
Personal hx of cancer	26	7.00	234	7.40	11.11
Personal and Family Hx	282	76.00	2215	70.05	12.73
BMI (± 30 days of date of gene panel testing, kg/m^2)					
Underweight (< 18.5)	3	0.90	39	1.46	7.69
Normal (18.5–24.9)	114	34.23	858	32.06	13.29
Overweight (25–29.9)	89	26.73	831	31.05	10.71
Obese (> 30)	127	38.14	948	35.43	13.40
Missing	38	NA	486	NA	NA
Geocoded education (% high school graduate and above)					
0–50%	21	7.64	157	6.37	13.38
51–75%	58	21.09	473	19.18	12.26
76–100%	196	71.27	1836	74.45	10.68
Missing	96	NA	696	NA	NA
Charlson index (in year of gene panel testing)					
0	145	39.08	1419	44.88	10.22
1 or 2	115	31.00	936	29.60	12.29
3 or more	111	29.92	807	25.52	13.75
Ethnicity					
African	32	8.72	319	10.19	10.03
Ashkenazi	19	5.18	127	4.06	14.96
Asian	42	11.44	415	13.26	10.12
Central/Eastern Europe	24	6.54	173	5.53	13.87
Latina/Hispanic	122	33.24	1008	32.20	12.10
Native American	20	5.45	158	5.05	12.66
Near east/Mideast	14	3.81	101	3.23	13.86
Western/Northern Europe	156	42.51	1316	42.04	11.85
Unknown/missing	4	NA	32	NA	NA

PV/LPV prevalence overall and by race/ethnicity and cancer site

Of the 3162 women, 371 (11.7%) had PV/LPV results for at least one of the 20 tested genes, 1889 (59.7%) were negative, and 902 (28.5%) had at least one variant of uncertain significance (VUS). The PV/LPV prevalence was lower in older women (> 60 years, 10.2%) compared to younger women (< 40 years, 12.8%) and in women with fewer comorbidities (10.2%). The highest PV/LPV prevalence was observed in women with Ashkenazi ancestry (14.9%), followed by Central/Eastern Europe (13.9%), Near-east/Mideast ethnicity (13.9%), Native American (12.7%), and Latina (12.1%). Women with African (10.0%) and Asian (10.1%) ethnicities had the lowest prevalence (Table 1). Of the 3162 women in the cohort, 2464 (77.9%) had a personal cancer history; the most common tumors were breast (75.1%), ovary (8.5%), and colon/rectum (4.3%) (Table 2). As expected for this cohort, the prevalence of PV/LPV results was the highest among women with breast cancer (68.3%), followed by ovarian cancer (12.9%) and colorectal cancer (5.9%).

Table 2 Distribution of all cancers by mutation status among patients with at least one record of cancer history

Anatomic site	Pathogenic/likely pathogenic variant		Negative		VUS		Total		PV/LPV prevalence
	N	%	*N*	%	*N*	%	*N*	%	%
Breast	218	68.34	1072	74.19	567	80.08	1857	75.12	11.74
Lung and bronchus	0	0.00	6	0.42	2	0.28	8	0.32	0.00
Colon and rectum	19	5.96	62	4.29	25	3.53	106	4.29	17.92
Uterine corpus	13	4.08	50	3.46	21	2.97	84	3.40	15.48
Lymphoma	0	0.00	5	0.35	1	0.14	6	0.24	0.00
Melanoma of the skin	6	1.88	27	1.87	5	0.71	38	1.54	15.79
Thyroid	6	1.88	20	1.38	7	0.99	33	1.33	18.18
Ovary	41	12.85	121	8.37	48	6.78	210	8.50	19.52
Kidney and renal pelvis	1	0.31	13	0.90	1	0.14	15	0.61	6.67
Pancreas	4	1.25	4	0.28	3	0.42	11	0.44	36.36
Stomach	2	0.63	7	0.48	5	0.71	14	0.57	14.29
Other sites	9	2.82	53	3.67	20	2.82	82	3.32	10.98
Total	319		1440		705		2464		12.95

PV/LPV prevalence among different genes

In women with any PV/LPV result, the most common mutations were in *BRCA1/2* ($n = 175$ mutations, 5.5%), *MUTYH* ($n = 67$, 1.6%), *CHEK2* ($n = 45$, 1.4%), and *ATM* ($n = 34$, 1.2%) genes (Fig. 1). In this subset, roughly 6.3% of women had at least one mutation in genes other than *BRCA*.

Distribution of mutations by cancer history status

We reviewed medical records of the 371 women with any PV/LPV result to confirm personal cancer and family cancer history. In these 371 women, the distribution of mutations in the four major groups of genes (*BRCA1/2*; other breast cancer susceptibility genes; Lynch syndrome; other genes) was generally similar in women with or without a personal cancer

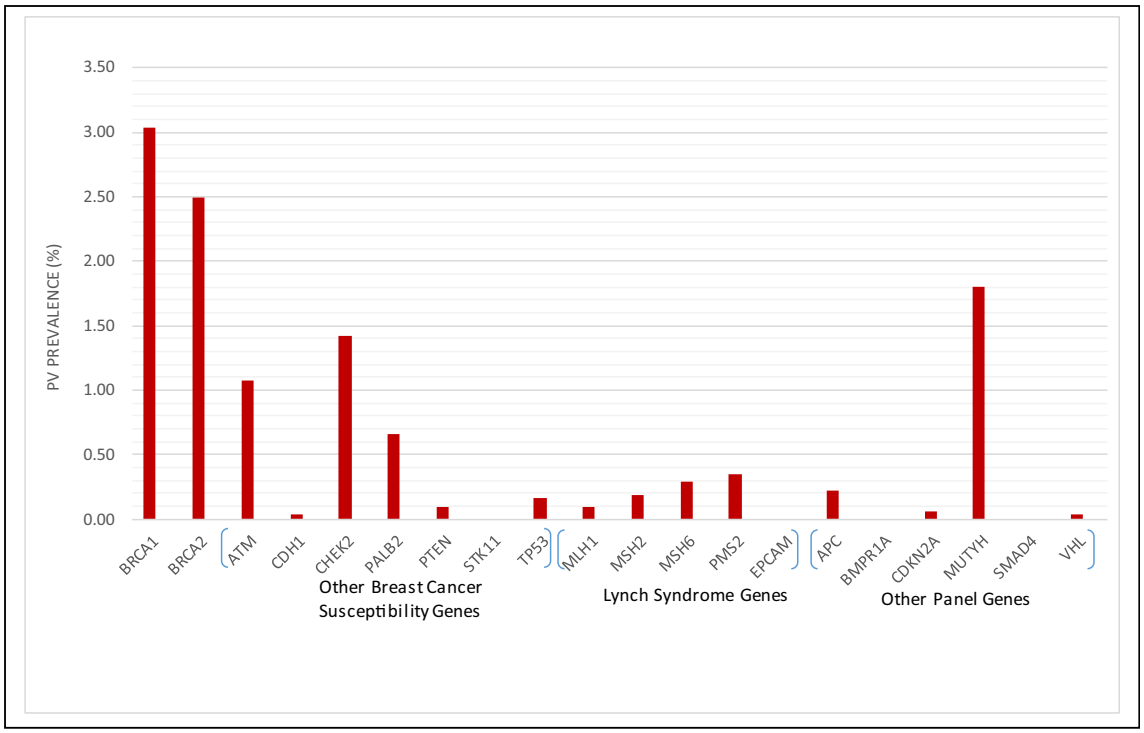

Fig. 1 Prevalence of pathogenic or likely pathogenic variants (PV/LPV) by clinical characteristics ($N = 3162$ women)

history (Fig. 2). In women with a mutation, *BRCA1/2* accounted for 45.0% of the total mutations; this reflects the predominant reason for referral, which was a personal history of breast cancer. The overall proportion of non-*BRCA* mutations was 55.0%. Specifically, the second largest group of mutations was in non-*BRCA* genes that are also implicated in breast cancer (*ATM, CDH1, CHEK2, PALB2, PTEN, TP53*); these genes accounted for 29.0% of the total mutations in women. Roughly 8.0% of the total mutations occurred in Lynch syndrome genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*), although we found no PV/LPV results in these genes in the 23 women with only a personal history of cancer. The remaining 18.0% of the total mutations were in other panel genes ($n = 67$): 7 in the *APC* gene, 2 in *CDKN2A*, 1 in *VHL*, and 57 in *MUTYH*. Mutations in MUTYH are inherited as a recessive disorder (and increases the risk of MUTYH-associated polyposis and colorectal cancer), thus, the charts of all 57 subjects identified as MUTYH mutation carriers were reviewed; none carried two mutations. One subject's mutation was subsequently reclassified as a VUS. Only one subject had a personal history of colon cancer (rectal adenocarcinoma diagnosed at 54 years of age), but she had no family history of colorectal cancer. Twelve other MUTYH mutation carriers had a family history of colon cancer, but none of those family members were genotyped to our knowledge.

Prevalence of VUS results in the full cohort

In the full cohort of 3162 women, variants of unknown significance (VUS) were found in 902 subjects (28.5%). The most frequent VUS results were found in *ATM* ($n = 232$, 13.6%), *APC* ($n = 188$, 16.8%), *BRCA2* ($n = 121$, 8.8%), and *MSH6* genes ($n = 113$, 8.2%) (data not shown).

Associations between clinical characteristics and PV/LPV results

Compared to women with both personal and family history of cancer, those with family history *only* were about 30% less likely to have PV/LPV results in non-*BRCA* genes (adjusted OR = 0.67, 95% CI 0.45, 1.01), but results were not statistically significant and may be due to the referral pattern for genetic counseling and testing (Table 3), after adjusting age at testing and race/ethnicity. Latina/Hispanic women were half as likely to have PV/LPV results in non-*BRCA* genes associated with breast cancer (adjusted OR = 0.53, 95% CI 0.33–0.85). Age at testing was not associated with mutations in non-*BRCA* genes.

Clinical management of patients with PV/LPV results

To determine how patients are tracked following a PV/LPV result (but without a personal cancer history), we reviewed electronic health records (EHR) of a subset of patients to determine their cancer risk management and healthcare decisions. We reviewed the medical records of 49 women who did not have a personal cancer history prior to being identified with a PV/LPV in a breast cancer predisposition gene. This group included 17 *BRCA1* mutation carriers, 12 *BRCA2* mutation carriers, 8 *ATM* carriers, 7 *CHEK2* carriers, 4 *PALB2* carriers, and 1 *PTEN* carrier. The women range from 25 to 82 years of age and were all alive at last follow-up. In the 42 to 64 months since these women completed the cancer gene panel, all except for one received appropriate screening tests including mammograms and/or breast magnetic resonance imaging (MRIs) for breast cancer screening, were offered pelvic ultrasound/*CA125* for ovarian cancer (*BRCA1/2* mutation

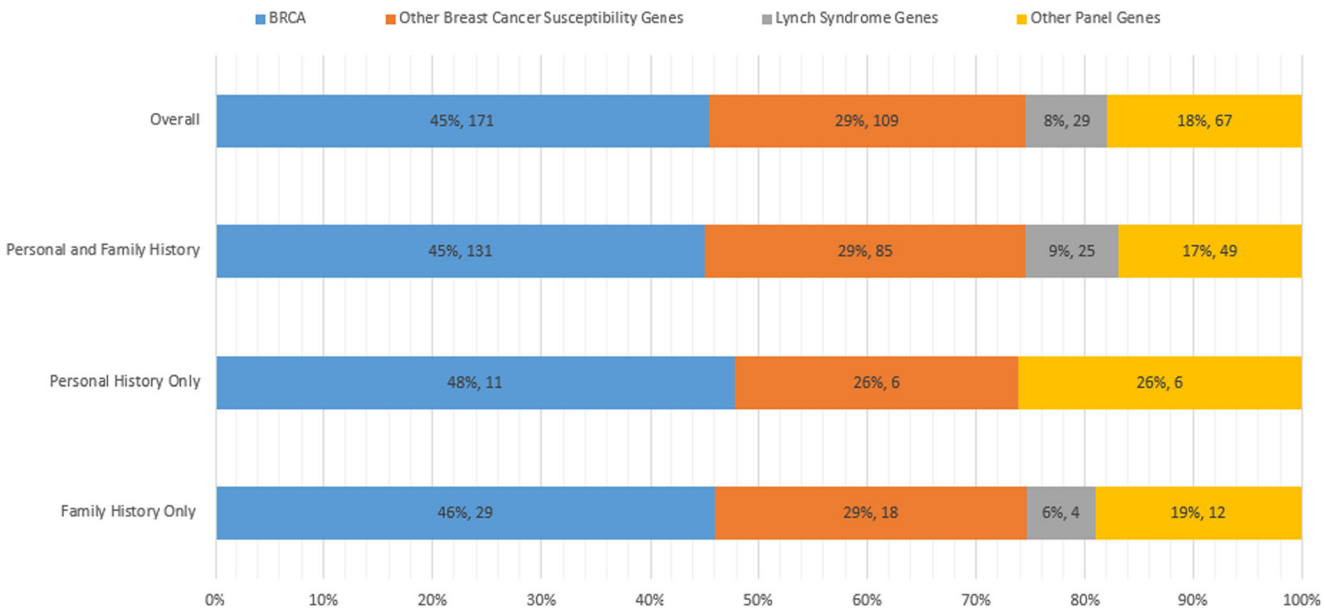

Fig. 2 Distribution of mutations (%, *N*) among women with PV/LPV results by personal and family history of cancer ($N = 376$ mutations in 371 women)

Table 3 Factors correlated with mutation in genes other than BRCA

Mutation(s)	Any non-BRCA gene OR (95% CI)	Other breast cancer susceptibility genes OR (95% CI)	Lynch syndrome genes OR (95% CI)	Other panel genes OR (95% CI)
Latina/Hispanic				
Yes	0.78 (0.56, 1.08)	0.53 (0.33, 0.85)	1.46 (0.71, 3.00)	1.13 (0.67, 1.90)
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Age at testing				
< 40	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
40–49	0.91 (0.59, 1.40)	1.07 (0.60, 1.92)	0.79 (0.26, 2.34)	0.62 (0.29, 1.33)
50–59	1.12 (0.72, 1.74)	0.98 (0.53, 1.81)	1.15 (0.40, 3.33)	1.29 (0.64, 2.59)
60+	0.83 (0.52, 1.32)	0.79 (0.42, 1.47)	0.92 (0.30, 2.80)	0.79 (0.37, 1.72)
History of cancer				
Family hx of cancer	0.67 (0.45, 1.01)	0.63 (0.37, 1.09)	0.53 (0.19, 1.46)	0.73 (0.37, 1.43)
Personal hx of cancer	0.97 (0.55, 1.69)	0.68 (0.29, 1.60)	0.18 (0.01, 2.74)	1.20 (0.50, 2.88)
Both (personal and family hx)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

Models adjusted for age group at testing, Latina/Hispanic (yes/no), and history of cancer (family/personal/both)

carriers), or they completed risk-reducing surgery or surgical consultation to explore clinical options. The one woman who did not complete follow-up left our healthcare system shortly after completing the gene panel test. A total of 6 women have been diagnosed with cancer thus far: 2 BRCA1 carriers developed fallopian tube cancer, 3 BRCA2 carriers developed breast cancer (one DCIS), and 1 ATM carrier developed thyroid cancer. Of note, the diagnosis of DCIS was made on pathology examination of a prophylactic bilateral mastectomy specimen. A total of 16 women with a *CDH1* mutation were identified and had been followed up with a gastroenterology consultation possibly for endoscopy procedures.

Discussion

This study examined use of multigene testing in one of the most diverse community-based cohorts of patients in the USA (about 60% of the cohort was minority women) who were tested via the same multigene panel. Given that more than half of our PV/LPV results were in genes other than *BRCA1/2* in referred women regardless of their personal or family cancer history, our results suggest that cancer panel testing is an appropriate method for detecting germline mutations in a high-risk cohort in a managed care setting. Other reports also support the utility of cancer gene panels in real world clinical settings (LaDuca et al. 2014; Tung et al. 2015). In the group with a personal cancer history (mainly with suspected hereditary breast cancer), the proportion of *BRCA1/2* mutations in this referral population was about 45%, consistent with the role of *BRCA1/2* genes in hereditary breast cancer. The over-representation of *BRCA1/2* among all mutations identified likely reflected a greater proportion of patients referred for genetic counseling whose personal and/or family history included breast cancer compared to other cancers. Although not all the genes included in the 20-gene panel were relevant to each subject's personal cancer history, overall the use of the panel identified a significantly higher number of PV/LPV results in patients with a personal history of cancer than testing only *BRCA1* and *BRCA2* genes. Further, in our diverse cohort, we determined that the PV/LPV prevalence varied from 10 to 15% across all the race/ethnic groups in this referred population. Further, we found that women who lived in areas with higher geocoded education were more likely to undergo testing.

Because the cost of multigene testing decreased after 2013 (when the US Supreme Court overturned patents on genes), and given the development of next generation sequencing technology, our study (as well as other recent reports (Beitsch et al. 2019) suggest that expansion of multigene testing to all women recently diagnosed with cancer may be feasible. As additional evidence accrues regarding the actionability of the mutations in non-*BRCA* genes, such knowledge can be used for the clinical management of breast cancer survivors or to inform decision-making as to whether unaffected family members should be tested to enable prevention of hereditary cancers (for example, through enhanced screening for those at high-risk for breast cancer or consideration of risk-reducing surgeries for ovarian cancer for certain women). However, more data on the costs, risks and benefits of testing, healthcare resources needed, and effect of multigene testing on long-term health outcomes are required before clinical recommendations are implemented to expand testing.

We found a surprisingly large proportion of VUS results, given that our panel included only high/moderate risk cancer genes and excluded poorly characterized genes. However, as

more data accumulate on the prevalence of variants in specific ethnic groups and on clinical outcomes of multigene panel testing, we anticipate the VUS proportions will decrease in the future, as more variants are classified as pathogenic or benign. At this time, we continue to track patients with VUS results in a database for monitoring and in anticipation of future re-classification.

To our knowledge, this is one of the first studies to report on implementation of multigene cancer panel testing in a single community-based health plan. Most of the prior studies were based on patients recruited from multiple academic centers who underwent different panel tests performed by various laboratories, only included personal or family history data from laboratory requisition forms, or included patients from healthcare settings that did not have consistent guidelines for testing. Such settings make characterization of the source population difficult to infer. Hence, these prior studies may have even greater limitations regarding generalizability of results to the broader population.

Our study has several strengths. Members were all insured and received similar care within an integrated healthcare delivery system. All patients underwent genetic counseling by the health plan's licensed genetic counselors or clinical geneticists, and clinical data (demographics, comorbidities, personal cancer history and family history) were collected from actual EHR, not genetic test requisitions. This enhances internal validity of our results. All patients also underwent testing with the same gene panel, ensuring the comparability of the results by history of cancer. Importantly, unlike other studies, our study population was diverse and included 57% of women from various ethnic origins.

Certain limitations must also be considered. For example, we did not capture information on those who declined testing; however, our previous clinical experience with *BRCA1/2* testing indicated that approximately 85 to 90% of patients accepted cancer genetic testing when it is offered by our genetics providers. On the other hand, because of the managed care plan and the diverse cohort, our results may not be generalizable to other healthcare settings. Although we did not test for genetic ancestry, we extracted race/ethnicity and family history data based on detailed genetic counseling notes and pedigrees. In addition, given that the study population only included members referred for genetic counseling, the PV/LPV prevalence may not be generalizable to the larger community of southern California residents. Another limitation is that we could not review each of the pedigrees from patients who had mutations in genes other than the main breast cancer-associated genes. This would have required in-depth subject-by-subject chart review which was beyond the scope of this study. We also did not assess penetrance of the genes given the small numbers of subjects with each mutation (the calculation would not have been statistically robust, e.g., we only had $N = 45$ patients with a *CHEK2* mutation). Further, given the expected high prevalence of VUS, a detailed analysis of the types of variants (missense, splice-site, frameshift) was not pursued, as these variants are not entered into our molecular testing database. Accordingly, identification of recurrent variants was not sought. Because testing family members for VUS is generally discouraged, and multiple affected family members were generally not available to us, there were no attempts at segregation analyses. Evaluation for pathogenicity of the variants was limited to the characteristics provided by the external laboratory vendor (evolutionary conservation, prevalence in large cohorts, analyses by multiple predictive software programs, etc.). Additionally, we could not quantify the numbers of family members with a cancer history as these data, as well as cancer sites, and the ages of diagnoses among relatives are not available in the index patient's electronic medical records.

Our future work entails examining mutation frequencies in a larger group once more members have undergone genetic counseling and testing with the same panel. Furthermore, linkage with the members' EHR will enable us to examine long-term outcomes and follow-up procedures. As more natural history data are compiled about less well-characterized cancer genes, we also anticipate the following: (a) expanding the scope of cancers implicated with specific genes, (b) encountering fewer VUS, and (c) developing additional gene-specific surveillance protocols to enable early cancer detection in high-risk patients and their family members. Additionally, a cancer genetics database and EHR also enable us to conduct cascade testing of unaffected relatives after a mutation is identified in the index patient. We are intrigued by the finding that a higher proportion of Latina/Hispanic women were referred for and tested for hereditary breast and ovarian cancer (33.0%) in this cohort than in our overall population of breast cancer patients (10.0%). Reasons for this are unclear; however, we are exploring potential contributions of biological, demographic, and clinical factors. Future studies should also consider contacting patients and their family members regarding specific patterns of cancers in those with a family history but without mutation, which may be suggestive of new syndromes.

In summary, our results suggest that even in a population of patients referred mostly for suspected hereditary breast and ovarian cancer, a multigene cancer panel will identify a significant proportion of mutations in genes other than *BRCA*1/2. Further, in an EHR review of a subset of patients with PV/LPV results, but without a cancer diagnosis, we determined that patients received appropriate screening or risk-reducing procedures. Thus, this study suggests that multigene cancer panels influenced cancer risk management decisions of these patients in the managed care setting.

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Compliance with ethical standards

Conflict of interest Kaiser Permanente Southern California (KPSC) received a grant from GeneDx to support conference travel for Mónica Alvarado, MS LCGC and Reina Haque, PhD.

George E. Tiller, MD PhD and Joanie Chung, MPH declare no conflict of interest.

Ethical approval The study was reviewed and approved by the KPSC Internal Review Board. All procedures followed the standards of the KPSC IRB and with the 1975 Helsinki Declaration, and its later amendments or comparable ethical standards. The KPSC IRB waived informed written consent for this observational data-only study.

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