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blood advances

Patient perspectives on testing for clonal hematopoiesis of indeterminate potential

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Key Points

- Many young breast cancer survivors are interested in CHIP testing, with preferences varying by risk communication and actionability.
- Learning of CHIP and its associated risks may elicit significant anxiety, requiring provider awareness and specific care.

Clonal hematopoiesis of indeterminate potential (CHIP), an emerging biomarker for personalized risk-directed interventions, is increased in cancer survivors. However, little is known about patient preferences for CHIP testing. We surveyed participants in a prospective cohort study of young women with breast cancer (BC). The emailed survey included an introduction to CHIP and a vignette eliciting participants' preferences for CHIP testing, considering sequentially: population-based 10-year risk of BC recurrence, hematologic malignancy, and heart disease; increased CHIP-associated risks; current CHIP management; dedicated CHIP clinic; and hypothetical CHIP treatment. Preference changes were evaluated using the McNemar test. The survey response rate was 82.2% (528/642). Median age at time of survey was 46 years and median time from diagnosis was 108 months. Only 5.9% had prior knowledge of CHIP. After vignette presentation, most survivors (87.1%) recommended CHIP testing for the vignette patient. Presented next with CHIP-independent, population-based risks, 11.1% shifted their preference from testing to not testing. After receiving information about CHIP-associated risks, an additional 10.1% shifted their preference to testing. Preference for testing increased if vignette patient was offered a CHIP clinic or hypothetical CHIP treatment, with 7.2% and 14.1% switching preferences toward testing, respectively. Finally, 75.8% of participants desired CHIP testing for themselves. Among participants, 28.2% reported that learning about CHIP caused at least moderate anxiety. Most young survivors favored CHIP testing, with preferences influenced by risk presentation and potential management strategies. Our findings highlight the importance of risk communication and psychosocial support when considering biomarkers for future risk in cancer survivors. This trial has been registered at www.clinicaltrials.gov as #NCT01468246.

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The data sets used and/or analyzed during this study are available on request from the corresponding author, Ann Partridge (ann_partridge@dfci.harvard.edu), and in accordance with Dana-Farber/Harvard Cancer Center Institutional Review Board approval.

The full-text version of this article contains a data supplement.

Introduction

Clonal hematopoiesis is a condition in which somatic mutations in hematopoietic stem cells drive the expansion of a clonal population of blood cells that is detectable using next-generation sequencing.[1,2] Clonal hematopoiesis not only reflects malignant conditions, such as acute myeloid leukemia and myelodysplastic syndrome, but is also found in individuals without hematologic disease. In such cases, when the detected mutation occurs in a gene recurrently mutated in myeloid neoplasia and is present with ≥2% mutant allele fraction in the peripheral blood, it is termed clonal hematopoiesis of indeterminate potential (CHIP).[3] CHIP is a common, age-related phenomenon in the general population.[1-3] Though having CHIP significantly increases the risk of evolution to hematologic malignancy, the increased mortality observed in patients with CHIP is largely driven by nonmalignant adverse outcomes, particularly ischemic cardiovascular disease (CVD).[1,2,4]

Compared with age-matched controls, individuals with a history of cancer have significantly higher rates of CHIP, largely driven by the receipt of cytotoxic therapy and shared risk factors between cancer and CHIP (eg, smoking).[5-7] Overall, patients with cancer with CHIP have reduced overall survival, a higher risk for developing therapy-related myeloid neoplasms, and an increased incidence of CVD among cancer survivors.[5-8] In patients with solid tumors, CHIP is often incidentally found during routine clinical sequencing, including germ line genetic testing and somatic tumor profiling, but may also be identified as part of a diagnostic workup for cytopenias.

There is growing interest in using CHIP as both a prognostic and predictive biomarker for hematologic and nonhematologic adverse outcomes to mitigate CHIP-associated risks, particularly in cancer survivors.[7-11] Identifying CHIP may be especially useful in cancer survivors who have higher rates of CHIP (due to receipt of cytotoxic therapy) and extended exposure to the long-term risks of CHIP. Young women with stage 0-III breast cancer (BC) represent such a group as they have relatively high rates of long-term, disease-free survival after treatment with multiple modalities, including surgery, combination chemotherapy, radiation, hormonal therapy, and targeted agents.[12] To date, studies have yet to show that long-term outcomes can be improved by targeting specific interventions in those with CHIP. However, while such populations may ultimately benefit from efforts to identify CHIP and many institutions have established "precursor clinics" or "CHIP clinics," studies to date have largely focused on CHIP itself, not the individuals who have it, and as such have failed to rigorously assess patient perspectives. For example, whether patients experience substantial anxiety and distress after learning they have CHIP remains unknown, particularly among young adult cancer survivors who have already had a potentially traumatic medical experience with long-term repercussions.[13,14]

To inform the decision-making process regarding whether and how to implement CHIP testing in cancer survivors, we surveyed young BC survivors participating in an ongoing prospective observational cohort. We hypothesized that similar to preferences surrounding the discovery of germ line mutations, patients' interest in learning about CHIP would be high overall but dependent on the perceived associated risks and actionability of the findings.[15,16]

Methods

Study population and survey administration

The survey was designed as a 1-time cross-sectional substudy of the Young Women's Breast Cancer study (YWS, #NCT01468246), a multicenter prospective cohort that enrolled English-speaking women newly diagnosed with BC aged ≤40 years, between 2006-2016 from 13 academic and community health care institutions in the United States (Colorado, Massachusetts, Minnesota, and New Hampshire) and Canada.[17] Participants were surveyed every 6 months for the initial 3 years after diagnosis and then annually with an array of questionnaires regarding sociodemographic and medical history and multiple patient-reported clinical and quality of life outcomes. The survey data were supplemented with data extracted from medical record review, central histopathologic review, and prospectively collected tissue and blood specimens. YWS participants diagnosed with primary stage 0-III BC, who agreed to participate in future research, and who were alive were eligible for the current substudy. The exclusion criteria included documented, recurrent metastatic BC, new primary non-BC, participation in CHIP focus groups, and no documented email address. Self-reported BC recurrences and nonbreast primary cancers were confirmed through a review of medical records. The survey was distributed through email and completed in Research Electronic Data Capture, between 21 September 2020 and 14 December 2020. The study was approved by the Dana-Farber Cancer Institute Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Survey development

As there were no existing validated instruments to evaluate preferences and concerns regarding CHIP testing, we developed a survey using hypothetical risk scenarios and assessed patient preferences based on our previous research.[14,18-24] This survey was then informed by a focus group study (Dana-Farber/Harvard Cancer Center protocol #19-412), which included 4 groups with a total of 28 participants diagnosed with early BC before age 45 and within 10 years of diagnosis without metastatic recurrence. The resulting survey was then piloted among a group of advocates for patients with BC and adapted based on their feedback. As this was planned to be a 1-time exploratory survey, we did not conduct additional rigorous survey methodology validations. The final 56-item survey (Appendix 1) included an initial evaluation of participants' prior knowledge of CHIP, followed by a brief introduction to CHIP, its epidemiology, including the increased prevalence among patients with cancer, particularly after chemotherapy and/or radiotherapy, and known associated long-term outcomes. Participants were then introduced to a vignette describing a woman aged 47 years, with a history of stage II BC, previously treated with curative surgery, adjuvant chemotherapy, radiotherapy, and hormonal therapy, and now, 10 years after diagnosis, offered CHIP testing (Appendix 1). Population-based risks for BC recurrence,[25] heart disease,[26] and blood cancers[27] were estimated using clinical calculators and literature, and communicated as percentages and through pictographs. Participants were asked to indicate their preferences for CHIP testing for the woman in the vignette ("If you were Diane, would you want to get tested for CHIP?") on a 4-point Likert scale (ie, definitely test, probably test, probably not test, or

definitely not test) in a series of sequential scenarios considering (1) population-based 10-year risk of BC recurrence, hematologic malignancy, and heart disease; (2) estimated increase in these risks with CHIP; (3) currently available CHIP management with an expectant strategy, including blood draws and management of cardiovascular risk factors such as hypertension and hypercholesterolemia;[3,10,28,29] (4) a dedicated CHIP clinic;[28,29] and (5) a hypothetical CHIP treatment. Subsequent questions assessed participants' interest in CHIP testing for themselves (outside of the vignette) and their preferences regarding discussion of CHIP, disclosure of results, and potential follow-up, treatment, and support options. Questions about the perceived risks and benefits of CHIP testing were adapted from a similar survey concerning somatic tumor genomic testing.[30] Lastly, participants were asked to rate whether they experienced increased anxiety after learning about CHIP and its associated risks (none, mild, moderate, severe, or very severe).

Demographic and clinical data collection

To limit survey length and redundancy with prior surveys, participants demographic and clinical data were extracted from the YWS. Race, ethnicity, education, and financial comfort[31-33] were self-reported and defined according to the baseline YWS survey. Race was self-reported by study participants as American Indian or Alaska Native; Asian, Black, or African American; White; or multiracial. Ethnicity was self-reported as either Hispanic/Latino or not. When unavailable via survey self-report, race and ethnicity were abstracted from the medical records. The BC stage at diagnosis was defined through a review of the pathology reports and medical records. Receipt of chemotherapy and/or radiotherapy for primary BC and previous germ line genetic testing were determined from surveys in combination with a medical record review.

Statistical analysis

The participants' demographic and clinical data and survey responses were reported using descriptive measures. Counts and proportions were calculated for the categorical variables. The means and standard deviations were summarized as continuous variables. The characteristics of the survey responders were compared using *t* tests for continuous data and Fisher exact test for categorical data. CHIP testing preferences were dichotomized as inclined (definitely test or probably test) or not inclined to be tested (definitely not test or probably not test). Changes in CHIP testing preferences before and after the vignette scenarios were evaluated using the McNemar test with a type I error rate of 5%. With 600 anticipated respondents, assuming that 20% of the participants would change their preferences toward CHIP testing in response to different scenarios, the study had 91% power to distinguish the difference between an alternative of 13% of the women shifting their preferences toward seeking CHIP testing in response to presented risks and management strategies and a null of 7% shifting away from seeking CHIP testing, that is, 5% more women shifting their preference toward testing after being exposed to the scenario. A secondary, nonprespecified analysis was performed to evaluate participant characteristics associated with a personal inclination for CHIP testing using univariable and multivariable stepwise logistic regression. All variables lower than the 2-sided type I error of 0.05 were considered statistically significant throughout. Analyses were conducted using R software version 4.0.4.

Results

Participants' characteristics

Of the 1302 women enrolled in the YWS, 642 were eligible and were contacted through email for participation in this substudy (Figure 1). Eighty-two percent (528/642) of the participants responded to the survey, with 93% (491/528) submitting a complete survey and 7% submitting a (37/528) a partially complete survey. Eighteen of those who only partially completed the survey discontinued the survey immediately after the introductory explanation of CHIP. Survey responders were more financially comfortable at diagnosis than nonresponders (54.2% vs 40.4%, $P = .028$) but were similar with respect to all other demographic and disease characteristics (supplemental Table 1).

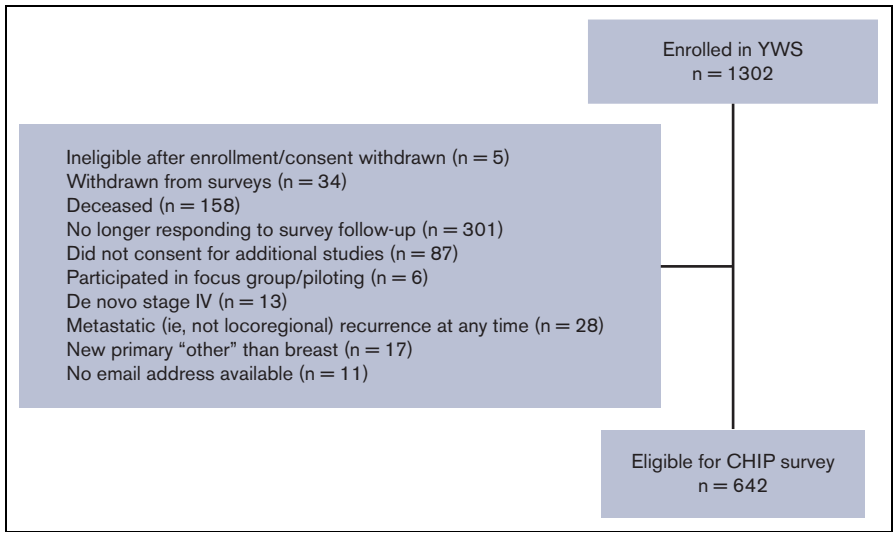

Figure 1. Flowchart of study population.

The participants' median age at the time of survey was 46 years (range, 31-54), and the median time from diagnosis was 108 months (range, 60-168); 88.4% were White, and 90.9% were non-Hispanic (Table 1). Most participants had stage I-II BC (78.8%) and received chemotherapy (73.1%) and/or adjuvant radiotherapy (62%). The results of prior clinically performed germ line genetic testing were available for 89% of the participants, and 14% had a clinically significant mutation. Of these, mutations were most commonly found in *BRCA1* (40/71), *BRCA2* (21/71), and *TP53* (3/71) genes.

Interest in CHIP testing

Only 5.9% (31/528) of the responders had heard of CHIP before the survey. Responses regarding interest in CHIP testing after the introduction of CHIP and patient-centered vignette series are presented in Table 2. Following the initial vignette presentation, most participants (87.1%, 460/528) recommended CHIP testing for the vignette patient. Recommendations for testing significantly decreased to 76.7% (405/528) when they were informed of CHIP-independent, population-based risks for heart disease, blood cancers, and BC recurrence, with 11.1% (56/504) of the participants shifting their preference from inclined to CHIP testing to not inclined, compared with only 0.6% (3/504) who switched their preference from not inclined to inclined ($P < .001$). However, after being presented with the estimated increase in risk for heart disease and blood cancers conferred by CHIP, interest in testing significantly increased to 85% (449/528), with 10.1% of the participants (51/503) shifting their preference to testing and 1.4% (7/503) switching their preference to not testing, compared with the prior scenario that showed population risks uninformed by CHIP status ($P < .001$).

Following the presentation of population risks and their increase in the setting of CHIP, we noted in the survey that treatment for CHIP is not currently available, and participants were asked how theoretical management strategies might impact their recommendations for CHIP testing of the patient in the vignette. When the currently available management approach for CHIP (an expectant strategy including blood tests and management of cardiovascular risk factors) was offered, 78.6% of the participants (415/528) were inclined to testing. Interest in testing significantly increased with the possibility of managing CHIP through a specialized clinic or with the availability of a hypothetical CHIP treatment, with 7.2% (36/502) and 14.1% (71/502) of the participants switching their preferences toward testing, respectively, compared with the current expert-recommended approach ($P < .001$ for both).

We subsequently assessed participants' personal preference regarding CHIP testing outside the vignette, and 75.8% (400/528) indicated an interest in CHIP testing for themselves. In univariate analysis (Table 3), less financial comfort at cohort enrollment (OR, 1.66; 95% CI, 1.05-2.67; vs more financial comfort), stage II disease (OR, 1.97; 95% CI, 1.18-3.32; vs stage I), receipt of chemotherapy (OR, 2.33; 95% CI, 1.45-3.71; vs not), and a personal history of a clinically significant germ line genetic variant (OR, 2.40; 95% CI, 1.12-5.95; vs not) were associated with personal preference for CHIP testing. In a multivariable-adjusted model, only receipt of chemotherapy (OR, 2.33; 95% CI, 1.45-3.71) and less financial comfort at enrollment (OR, 1.61; 95% CI, 1.01-2.61) remained significantly associated with inclination for testing.

Table 1. Characteristics of survey responders

Characteristics	Responders
N (%)	528 (82%)
Age at BC diagnosis, median (range), y	37 (17-40)
Age at survey, median (range), y	46 (31-54)
Race, n (%)	
White	467 (88)
Native American	2 (<1)
Asian	30 (6)
Black, Haitian, or African American	15 (3)
Multiracial	7 (1)
Other/unknown	7 (1)
Ethnicity, n (%)	
Hispanic	18 (3)
Non-Hispanic	480 (91)
Unknown	30 (6)
Financial comfort at diagnosis, n (%)	
Comfortable	286 (54)
Uncomfortable	216 (41)
Unknown	26 (5)
Education at diagnosis, n (%)	
Below college	20 (4)
College and above	486 (92)
Unknown	22 (4)
Cancer stage, n (%)	
0	50 (9)
I	194 (37)
II	222 (42)
III	62 (12)
Chemotherapy, n (%)	
Yes	386 (73)
No	134 (25)
Unknown	8 (1.5)
Radiotherapy, n (%)	
Yes	327 (62)
No	200 (38)
Unknown	1 (<1)
Genetic testing summary, n (%)	
Negative	370 (70)
Positive	71 (14)
VUS	28 (5)
Unknown	59 (11)

VUS, variant of uncertain significance.

In our introduction, we quoted the risk of CHIP to range between <1%, under the age of 40 years and up to 10% to 15% after the age of 65 years, and stated that ths risk for developemnt of CHIP may increase with exposure to chemotherapy or radiotherapy. Most participants estimated that their likelihood of harboring CHIP was low (8.3% very unlikely, 17.0% unlikely, and 49.1% neither likely

Table 2. Interest in CHIP testing for patient in an introductory vignette at baseline, after disclosure of population-based risks, followed by CHIP-related risks, and then potential management strategies

Interest in CHIP testing following presentation of…	Definitely not have the test, n (%)	Probably not have the test, n (%)	Probably have the test, n (%)	Definitely have the test n (%)	Not available, n (%)	Change in testing preference* compared with…	Switch from inclined to disinclined, n (%)	Switch from disinclined to inclined, n (%)	*P* value
Risks									
(1) Vignette alone	4 (0.8)	42 (8.0)	190 (36.0)	270 (51.1)	22 (4.2)	–	–	–	–
(2) CHIP-independent, population-based risks for BC recurrence, hematologic malignancy, heart disease	12 (2.3)	87 (16.5)	195 (36.9)	210 (39.8)	24 (4.6)	Vignette alone (1 vs 2)	56/504 (11.1)	3/504 (0.6)	<.001
(3) Increased CHIP-associated risks	7 (1.3)	47 (8.9)	171 (32.4)	278 (52.7)	25 (4.7)	CHIP-independent population-based risks for BC recurrence, hematologic malignancy, and heart disease (2 vs 3)	7/503 (1.4)	51/503 (10.1)	<.001
Actionability									
(4) Current management strategy	20 (3.8)	67 (12.7)	181 (34.3)	234 (44.3)	26 (4.9)	–	–	–	–
(5) CHIP clinic	13 (2.5)	44 (8.3)	190 (36.0)	255 (48.3)	26 (4.9)	Current management strategy (4 vs 5)	6/502 (1.2)	36/502 (7.2)	<.001
(6) Hypothetical treatment for CHIP	4 (0.8)	13 (2.5)	140 (26.5)	345 (65.3)	26 (4.9)	Current management strategy (4 vs 6)	1/502 (0.2)	71/502 (14.1)	<.001

*CHIP testing inclination for self-dichotomized as inclined (definitely test or probably test) or disinclined (definitely not test or probably not test).

nor unlikely); however, 20.1% (106/528) estimated their risk of CHIP as likely or very likely on a 5-point Likert scale.

Preferences regarding integration of CHIP to clinical practice

Participants' preferences regarding the discussion of CHIP, disclosure of CHIP testing results, and potential support are presented in Table 4. Many participants would be comfortable (quite a bit or very much) learning about CHIP through printed (62.7%, 331/528) or website-based information (60.2%, 318/528), whereas fewer participants endorsed the use of an in-clinic computer (13.3%). In-person conversations with various providers were largely preferred, particularly with an oncologist or cancer specialist (88.1%, 465/528). For sharing of individual CHIP testing results, in-person disclosure was preferred over electronic means (83.5%, 441/528 vs 40.0%, 211/528). If diagnosed with CHIP, many participants expressed interest in periodic communications (70.6%, 373/528), lifestyle modifications (79.5%, 420/528), annual blood tests (71.2%, 376/528), or a potential treatment (68.6%, 362/528); fewer were interested in meeting with a mental health provider (29.4%, 155/528), support groups (19.1%, 101/528), or participating in a clinical trial (28.4%, 150/528). The preferred setting for follow-up of CHIP was a breast oncology clinic (39.6%, 209/528), followed by a CHIP-focused clinic (32.8%, 173/528), a cancer survivorship clinic (12.3%, 65/528), or a primary care clinic (8.1%, 43/528).

Concerns and benefits of CHIP testing

We administered 10 questions to evaluate the participants' perceived concerns and benefits from CHIP testing (Table 5). Most participants somewhat or strongly agreed that knowing if they had CHIP would help them change their behaviors to reduce disease risk (70.8%, 374/528) or help them seek medical attention to reduce disease risk (77.1%, 407/528). However, 22.7% (120/528) of participants believed that learning they had CHIP would be "more than [they] could handle emotionally"; 54.5% (288/528) were concerned that they may discover a condition that they could not do anything about, and 30.9% (163/528) were concerned that they may learn about an increased risk for a disease that they did not want to know about. In addition, a relatively large proportion (45.5%, 240/528) were concerned about the potential costs related to CHIP testing and/or recommended follow-up.

Anxiety after learning of CHIP

Upon completion of the CHIP-related questions, participants were asked about how much anxiety learning about CHIP may have caused: 26.9% reported none, 37.9% mild, 24.4% moderate, 2.5% severe, and 1.3% very severe (with 7.0% not responding). Anxiety caused by learning about CHIP was significantly associated with participants' personal preference for CHIP testing, with only 52.6% (10/19) of women who reported severe or very severe anxiety after learning about CHIP expressing an interest in testing compared with 81.3% (382/470) of those who reported no, mild, or moderate anxiety ($P < .001$).

Discussion

Multiple studies have demonstrated CHIP-associated risks of hematologic malignancy and death due to CVD and increased

Table 3. Demographic and clinical characteristics associated with inclination for CHIP testing for self (n = 500)

Characteristics	Inclined, n (%)	Disinclined, n (%)	Univariable OR for inclination (95% CI)	*P* value	Multivariable OR for inclination (95% CI)	*P* value
N	400 (80)	100 (20)	–		–	–
Age at diagnosis, median (range), y	37 (17-40)	37 (26-40)	–	.959	–	–
Age at survey, median (range), y	46 (31-54)	46 (33-52)	–	.774	–	–
Mo from diagnosis, median (range)	108 (60-168)	108 (60-168)	–	.483	–	–
Race						
White*	359 (90)	85 (85)	–	–	–	–
Native American	2 (<1)	0 (0)	∞ (0-∞)	.983	–	–
Asian	18 (5)	9 (9)	0.47 (0.21-1.14)	.079	–	–
Black, Haitian, or African American	10 (3)	4 (4)	0.59 (0.19-2.20)	.385	–	–
Multiracial	6 (1)	1 (1)	1.42 (0.24-27.02)	.747	–	–
Other/unknown	5 (1)	1 (1)	1.18 (0.19-22.84)	.878	–	–
Ethnicity						
Hispanic	49 (12)	18 (18)	0.64 (0.36-1.17)	.134	0.62 (0.34-1.16)	.125
Non-Hispanic*	351 (88)	82 (82)	–	–	–	–
Financial comfort at baseline						
Comfortable*	205 (51)	65 (65)	–	–	–	–
Uncomfortable	173 (43)	33 (33)	1.66 (1.05-2.67)	.032	1.61 (1.01-2.61)	.050
Unknown	22 (6)	2 (<2)	3.49 (0.99-22.14)	.097	0.47 (0.07-3.70)	.418
Education at baseline						
College and above*	365 (91)	95 (95)	–	–	–	–
Below college	15 (4)	5 (5)	0.78 (0.29-2.45)	.640	0.69 (0.25-2.22)	.501
Unknown	20 (5)	0 (0)	∞ (0-∞)	.977	∞ (0-∞)	.984
Breast cancer stage						
0	32 (8)	15 (15)	0.69 (0.34-1.41)	.290	–	–
I*	137 (34)	44 (44)	–		–	–
II	184 (46)	30 (30)	1.97 (1.18-3.32)	.010	–	–
III	47 (12)	11 (11)	1.37 (0.67-2.99)	.401	–	–
Chemotherapy						
Yes	308 (77)	60 (60)	2.33 (1.45-3.71)	<.001	2.18 (1.35-3.49)	.001
No*	86 (22)	39 (39)	–	–	–	–
Unknown	6 (2)	1 (1)	2.72 (0.44-52.31)	.362	0.49 (0.02-12.65)	.618
Radiotherapy						
Yes	253 (63)	59 (59)	1.20 (0.77-1.88)	.416	–	–
No*	146 (37)	41 (41)	–	–	–	–
Unknown	1 (<1)	0 (0)	∞ (0-∞)	.982		
Genetic testing summary						
Negative*	274 (69)	78 (78)	–	–	–	–
Positive	59 (15)	7 (7)	2.40 (1.12-5.95)	.037	–	–
VUS	24 (6)	4 (4)	1.71 (0.64-5.94)	.335	–	–
Information not available or not tested	43 (11)	11 (11)	1.11 (0.57-2.36)	.767	–	–

CI, confidence interval; OR, odds ratio; VUS, variant of uncertain significance.
*Reference category.

prevalence of CHIP among patients with cancer, particularly those previously treated with chemotherapy or radiotherapy. Although CHIP is not yet modifiable, it is increasingly identified, usually incidentally, in patients with cancer, and active screening approaches have been proposed.[7-11,34] Despite these efforts and the proliferation of clinics dedicated to counseling and managing these patients, no prior studies have sought to evaluate patient attitudes and preferences regarding CHIP testing and surrounding supportive care needs. In a population of over 500 women diagnosed with early BC at a young age, we observed variations in the

Table 4. Participants' preferences regarding discussion of CHIP, disclosure of CHIP testing results, and potential support

	Not at all, n (%)	A little bit, n (%)	Somewhat, n (%)	Quite a bit, n (%)	Very much, n (%)	Not available, n (%)
How comfortable would you feel learning general information about CHIP in the following ways?						
Print or written information	25 (4.7)	55 (10.4)	89 (16.9)	152 (28.8)	179 (33.9)	28 (5.3)
Web-based information	22 (4.2)	43 (8.1)	111 (21.0)	157 (29.7)	161 (30.5)	34 (6.4)
Computer kiosk touch screen in a clinic	209 (39.6)	105 (19.9)	110 (20.8)	35 (6.6)	35 (6.6)	34 (6.4)
Discussion with a nurse	28 (5.3)	39 (7.4)	101 (19.1)	163 (30.9)	163 (30.9)	34 (6.4)
Discussion with a primary care physician	28 (5.3)	34 (6.4)	97 (18.3)	157 (29.7)	181 (34.2)	31 (5.9)
Discussion with a cancer specialist such as an oncologist	6 (1.1)	5 (0.9)	24 (4.5)	130 (24.6)	335 (63.4)	28 (5.3)
If you were tested for CHIP, how comfortable would you be learning results through the following modes?						
In-person disclosure of results	9 (1.7)	9 (1.7)	39 (7.4)	125 (23.7)	316 (59.8)	30 (5.7)
Disclosure of results by electronic means (email, portal, etc)	100 (18.9)	64 (12.1)	126 (23.9)	107 (20.3)	104 (19.7)	27 (5.1)
If you were found to have CHIP, how interested would you be in the following?						
A clinical trial testing a medicine for CHIP	77 (14.6)	87 (16.5)	173 (32.8)	86 (16.3)	64 (12.1)	41 (7.8)
A proven medicine for CHIP (if there was one)	17 (3.2)	28 (5.3)	79 (15.0)	158 (29.9)	204 (38.6)	42 (8.0)
Yearly blood tests to follow CHIP and its possible complications	12 (2.3)	20 (3.8)	80 (15.2)	170 (32.3)	206 (39.0)	40 (7.6)
Lifestyle recommendations to reduce other risk factors that may be related to CHIP	6 (1.1)	13 (2.5)	48 (9.1)	156 (29.5)	264 (50.0)	41 (7.8)
Personalized heart/blood disease risk estimates considering age and ethnicity	10 (1.9)	21 (4.0)	62 (11.7)	153 (2.9)	241 (45.6)	41 (7.8)
Peer-support groups	131 (24.8)	103 (19.5)	154 (29.2)	59 (11.2)	42 (8.0)	39 (7.4)
Communication to keep you up to date with recommendations for managing CHIP	8 (1.5)	29 (5.5)	74 (14.0)	167 (31.6)	206 (39.0)	44 (8.3)
Meeting with a social worker or other mental health provider to help manage stress this diagnosis may cause	105 (19.9)	89 (16.9)	137 (25.9)	89 (16.9)	66 (12.5)	42 (8.0)

Table 5. Participants' perceived concerns and benefits regarding CHIP testing

	Strongly disagree n (%)	Somewhat disagree n (%)	Neither agree nor disagree n (%)	Somewhat agree n (%)	Strongly agree n (%)	Not available n (%)
Finding out that I had CHIP would be more than I could handle emotionally	124 (23.5)	114 (21.6)	137 (25.9)	93 (17.6)	27 (5.1)	33 (6.2)
This information about one's future health risks is better left unknown	237 (44.9)	120 (22.7)	73 (13.8)	43 (8.1)	23 (4.4)	32 (6.1)
I am concerned about the test because it is new and hasn't been used widely	89 (16.9)	110 (20.8)	164 (31.1)	113 (21.4)	19 (3.6)	33 (6.2)
I am concerned that the test being so new prevents me from asking other patients about their experiences with it	154 (29.2)	96 (18.2)	136 (25.8)	92 (17.4)	15 (2.8)	35 (6.6)
The results will help me change my behaviors and reduce my disease risk	15 (2.8)	28 (5.3)	77 (14.6)	231 (43.7)	143 (27.1)	34 (6.4)
The results will help me seek medical attention and reduce my disease risk	9 (1.7)	17 (3.2)	62 (11.7)	230 (43.6)	177 (33.5)	33 (6.2)
I am concerned I could lose my job/insurance if the results get out	204 (38.6)	91 (17.2)	104 (19.7)	71 (13.4)	26 (4.9)	32 (6.1)
I am concerned about costs related to CHIP testing or recommended follow-up	95 (18.0)	57 (10.8)	104 (19.7)	149 (28.2)	91 (17.2)	32 (6.1)
I may learn that I have an increased risk for a disease that I did not want to know about	150 (28.4)	92 (17.4)	89 (16.9)	121 (22.9)	45 (8.5)	31 (5.9)
I may learn that I have a condition that I can do nothing about	68 (12.9)	62 (11.7)	78 (14.8)	203 (38.4)	85 (16.1)	32 (6.1)

proportion inclined to recommend testing a vignette patient for CHIP depending on the presentation of associated risks and potential management strategies. Regardless of these varying factors, interest in testing was consistently high, and over three-fourths of the women expressed an interest in having CHIP testing for themselves after learning of CHIP and completing the vignette-based part of the survey. Thus, for many young cancer survivors, CHIP status may be considered as personally relevant health information.

Similar information-seeking preferences have been reported in other young populations surveyed regarding their preferences for learning various types of germ line genome sequencing results.[15,16,35] In a comparable cohort of young women diagnosed with BC, aged ≤40 years, 77% were interested in learning results for variants that affect risk of preventable or treatable disease, and nearly two-thirds were interested in receiving carrier status results, usually not considered actionable; few (16%) were interested in learning about VUS results.[15] Similarly, in a cohort of patients with mixed cancers, many diagnosed at an early age (median age, 39; interquartile range, 15), whereas 93% agreed people would like to be informed about genetic conditions for which there is prevention or treatment that can modify cancer risk, 63% felt similarly about conditions for which there is no prevention or treatment.[35] Compared with older patients with BC, young patients are more often referred for genetic testing and diagnosed with conditions predisposing to cancer and thus may be acquainted with these issues, as they pertain to CHIP testing.[36] Indeed, most participants in our analysis underwent prior germline genetic testing. Nevertheless, interest in CHIP testing varied according to the presented risks and actionability, suggesting that, given a choice, women are likely to hold individualized testing preferences.

Participants who reported less financial comfort in their baseline survey upon enrollment in the YWS were more often interested in CHIP testing. This finding is surprising, given that 45% of the patients were somewhat to strongly concerned about costs related to CHIP testing or the recommended follow-up. In the setting of germline genetic testing, higher socioeconomic variables, such as income or education, are associated with an increased interest in and uptake of testing, although reports have not been consistent.[37,38] It is possible that within this young and educated cohort, some women may prioritize their health, even in the setting of subjective financial discomfort. Inherited disease-predisposing genetic mutations (ie, *BRCA1/2, TP53*) and CHIP differ significantly in their associated risks, inheritability, and management strategies, and further investigation of the association between socioeconomic factors and CHIP testing is warranted. In addition, financial comfort in YWS was evaluated at baseline, within 6 months of diagnosis, when the cohort's median age was 37 years, and was not revaluated in the current CHIP substudy survey (median age, 46 years). Regardless, for some patients, financial concerns may be a significant deterrent to the potential pursuit of CHIP testing, consultation, or follow-up.

Few participants had heard of CHIP before taking the survey. Anticipating this, we included in our survey a brief overview of CHIP and a vignette that illustrated how CHIP may influence health outcomes. Having more knowledge of testing benefits may be associated with an increased interest in genetic testing, and an informed consent process has been shown to improve such

knowledge.[15,39,40] Thus, the specific information we presented about CHIP and the way it was communicated may also be a driver of participants' high interest. The fact that prior treatment with chemotherapy, a risk factor for CHIP that we noted, was associated with an interest in CHIP testing may be suggestive of this. The information we delivered may also have shaped the participants' perceived concerns and benefits regarding CHIP testing. Although we explained that CHIP is age-related and rare in healthy individuals aged ≤40 years, 20% estimated their risk of CHIP as likely/very likely. Most participants agreed that CHIP results would help them change their behaviors (70.8%) or seek medical attention (77.1%) to reduce disease risk. Although these are not clear misconceptions, currently there are no available specific interventions proven to modify CHIP or its associated risks, beyond potentially optimizing standard cardiovascular risk factors.[41] The promise of new biomedical tests may be associated with inaccurate or unrealistic expectations.[30] Providers must make an effort to identify and adjust these beliefs when introducing novel biomarker tests, even for seemingly health-literate patients.

Nearly 30% of the survey participants stated that learning about CHIP and its associated risks elicited moderate or greater anxiety, with almost 4% reporting severe or very severe anxiety. Participants with more severe anxiety were significantly less likely to be interested in CHIP testing. Our surveyed population may have been more prone to anxiety given their previous cancer history and young age.[42,43] Notably, we did not offer patients an opportunity for clinical CHIP testing or the disclosure of results as part of this study.

Our presentation of CHIP may be analogous to conventional genetic counseling procedures, where patients are informed of their risks and advised about testing recommendations, with testing and results provided at a later date. Genetic counseling has largely been shown to improve knowledge of cancer genetics without a consequential adverse effect on affective outcomes, including anxiety.[44] While survey participants in our study were provided only general information about CHIP, most stated that they would prefer to hear about CHIP from a specialized provider and would be interested in individualized risk estimates and health recommendations, both routine features of genetic counseling. These strategies should be considered when offering CHIP testing or discussing results in clinical practice; they may help to alleviate some of the anxiety we observed and could facilitate testing in those with more severe anxiety. Attention will be required to identify individuals at particularly high risk of psychological distress who may need additional counseling and support after discussion of CHIP or when CHIP is diagnosed, particularly when discovered inadvertently, as is often the case in current practice. Care should be taken to ensure that patients are given a clear informed choice about being notified regarding findings of CHIP and other genetic risk markers, with no established interventions.

Several cancer centers have established CHIP clinics to provide counseling, clinical care, and monitoring for patients found to have CHIP and seek to develop new approaches to modify the hematologic and cardiovascular risks associated with CHIP.[28,29] Although the long-term benefits and clinical utility of such clinics remain unclear, many participants in our study favored referral to a specialized clinic if diagnosed with CHIP, underscoring the importance of expert counsel. This sentiment may be different, and potentially even higher, among a population without a cancer history, particularly when not already being actively followed at a cancer center when CHIP is diagnosed. Our findings provide pragmatic insight for such clinical approaches. Many patients may find being diagnosed with CHIP emotionally overwhelming, highlighting the importance of a multidisciplinary approach to the management of CHIP, including psychosocial professionals and incorporation of screening tools to identify those in need of their support. While some are weary that there may be no treatment for CHIP, many would seek medical attention or consider changing behaviors and may benefit from structured approaches for facilitating lifestyle change. We also found that individuals' decision-making around CHIP testing can be significantly influenced by their perception of the risks associated with CHIP. An emphasis on explaining CHIP and communicating its often low, but serious risks, will be crucial for these specialized clinics to promote participation in clinical trials and yet-to-be validated prevention strategies. As this testing is already happening and will likely be an inevitable part of future health care, it is also critical to ensure equitable access when designing these specialized clinics.

This research should be considered in the context of its limitations. The participants were all young women diagnosed with BC at age 40 or younger, thus limiting the generalizability of our findings to older populations and those with other cancers, which may be associated with a different prognosis. Similarly, participants were identified from an ongoing prospective research cohort, were predominantly White non-Hispanic, and had high levels of education. Ethnic minority groups are often underserved by genetic services and underrepresented in research.[45,46] Several of the suggested barriers to genetic testing in these populations may also apply to CHIP testing and require further research, such as low awareness and negative attitudes stemming from the anticipated emotional impact of test results, fear of discrimination, stigma, and an overall lack of trust in the health care system.[46,47] Culturally sensitive approaches involving multiple stakeholders will be needed to ensure adequate representation of minority populations in future efforts.[48] Given participants were surveyed several years after their primary diagnosis, responses may differ among patients closer to diagnosis. In addition, the participants completed the survey during the height of the COVID-19 pandemic and its associated restrictions. Survey responses could be influenced by the consequences of these events on mental health and general health perception.[49] Lastly, given the novelty of CHIP, we developed several measures for use specifically in this study and thus had not been previously validated. Our survey contained a significant educational component, with the potential to induce an acquiescence bias. Alternative approaches to preference elicitation or pretest education and risk estimation might have led participants to make different choices about CHIP testing.

In conclusion, this is the first study to show that many cancer survivors perceive CHIP testing as personally relevant health information. Variability in testing preferences exists and is influenced by presentation of risks related to CHIP and the availability of potential management strategies (ie, actionability). However, we must emphasize that our study should not be taken as an endorsement for all young BC survivors to be screened for CHIP nor does it aim to establish the risks and benefits of such. Additional epidemiological and clinical studies are needed before this approach can be considered. Our findings highlight the importance of effective counseling and adequate psychosocial support for those in need when considering potential clinical biomarkers of

future risks in cancer survivors. Further investigation of these areas in other patient populations, such as those diagnosed with CHIP, is warranted to inform how to best support patients, as they may increasingly be faced with incidental test results or offered CHIP testing in the future.

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Authorship

Contribution: T.S., G.G.F., P.G.M., C.J.G., S.M.R., C.S., B.L.E., and A.H.P. were responsible for the concept and design of the study; B.L.E. and A.H.P. acquired financial support; T.S., S.M.R., C.S., and A.H.P. were responsible for acquisition of study materials, participants, and data; T.S., G.G.F., S.M.R., D.S.N., and A.H.P. were responsible for analysis and interpretation of data; and all authors drafted the manuscript, tables, and figures and approved the manuscript as submitted and are accountable for all aspects of the work.

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