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Assessing Patient Attitudes Toward Genetic Testing For Hereditary Hematologic Malignancy

Addison Johnson

ASSESSING PATIENT ATTITUDES TOWARD GENETIC TESTING

FOR HEREDITARY HEMATOLOGIC MALIGNANCY

by

Addison Quinn Johnson, B.S.

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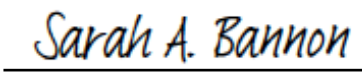

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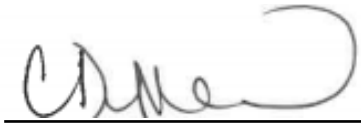

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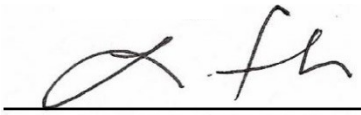

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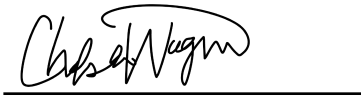

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ASSESSING PATIENT ATTITUDES TOWARD GENETIC TESTING FOR HEREDITARY HEMATOLOGIC MALIGNANCY

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by

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ASSESSING PATIENT ATTITUDES TOWARD GENETIC TESTING

FOR HEREDITARY HEMATOLOGIC MALIGNANCY

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Since 2003, more than 15 genes have been identified to predispose to hereditary hematologic malignancy (HHM). Although the diagnostic yield of germline analysis for leukemia is similar to solid tumors, referral for genetic evaluation in adults with leukemia is underperformed. Identifying HHM is important for prognostication, treatment, and donor selection for hematopoietic stem cell transplant. No studies have examined leukemia patients' attitudes toward genetic testing for HHM. This study aimed to assess leukemia patients' attitudes toward genetic testing and elicit current perceived distress due to a leukemia diagnosis. Data were elicited through an electronic survey sent to 5,513 patients diagnosed with a common acute or chronic leukemia, myelodysplastic syndrome, or aplastic anemia. Principal component analysis (PCA) was used to analyze patient attitudes; distress was measured through the Impact of Event Scale-Revised (IES-R). Associations of distress and attitudes toward genetic testing were assessed through multivariable regression analysis. 19.8% (1093/5513) of eligible respondents completed the survey. The majority reported interest in genetic testing for HHM (77%) and would choose to have genetic testing (78%). Slightly over half identified worry about cost (58%) or health insurance coverage (61%) of genetic testing as possible barriers. PCA analysis produced seven components regarding patient attitudes, identifying relevant themes of 1) interest in genetic testing for HHM, 2) impact on leukemia treatment, 3) discrimination and confidentiality, 4) psychosocial and familial impacts, and 5) cost of testing. The majority reported low distress with a median cumulative IES-R score of 7 (range 0-86). Furthermore, 18.5% (202/1093) of respondents reported a cumulative score of zero, indicating no distress. This large cohort of leukemia patients at various stages of treatment report overwhelming interest in genetic testing, concern about few barriers related to genetic testing, and relatively low distress due to a leukemia diagnosis.

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Introduction

Hematologic malignancies have long been considered sporadic cancers. In 2003, the first inherited form of acute myeloid leukemia (AML) was described, the *AML1/RUNX1* leukemogenesis pathway [1]. Since then, >15 genes have been identified as predispositions to acute and chronic leukemia, with the majority predisposing to myelodysplastic syndrome (MDS) and AML [2-4]. Despite growing awareness of hereditary hematologic malignancies (HHM), referral for genetic evaluation in adults with hematologic malignancies is underperformed [5]. Current studies indicate that the yield of germline analysis in leukemia patients suspected to have an underlying predisposition may range from 11-37% [5, 6].

Diagnosing an underlying HHM can identify syndrome-specific sequelae, refine treatment decisions, and inform the selection of donors for hematopoietic stem cell transplantation (HSCT) [7-12]. Professional experience and anecdotal evidence suggest that hematologist-oncologists may be hesitant to refer leukemia patients for genetic evaluation, when indicated, to avoid increasing distress. While there are no measures to prevent the development of leukemia, identification of at-risk individuals allows for disease surveillance, connection with psychosocial support resources, and anticipatory life and family planning [4]. The clinical benefits to germline analysis of HHM are apparent, yet the psychosocial and familial considerations which may inform attitudes toward genetic testing in individuals with leukemia, to our knowledge, have not been investigated.

Since genetic testing for hereditary breast and colorectal cancers became available in the early 1990s, research evaluating the attitudes of patients toward genetic testing for solid tumors has been performed. Motivations identified for genetic testing included understanding cancer risk in self and family members, making informed healthcare decisions, reducing uncertainty/anxiety, and regaining control. Concerns included worry for family members' risk, psychological distress after a positive result, guilt for passing on a mutation, and fear of discrimination based on genetic information [13-18].

It is possible that attitudes toward genetic testing in leukemia patients differ, given unique differences that arise due to a leukemia diagnosis. For example, leukemia patients with active disease or status-post donor HSCT cannot have genetic testing on peripheral blood due to disease contamination, or

donor DNA, respectively. Thus, genetic testing requires a skin punch biopsy to obtain DNA from cultured skin fibroblasts. While skin punch biopsies are generally considered safe and minimally invasive, patients with hematologic malignancies often have cytopenias which can cause concern for bleeding or infection risks from the procedure.

This study aims to characterize leukemia patients' attitudes, motivations, and barriers toward genetic testing for HHM, and elicit perceived distress due to their leukemia diagnosis. A deeper understanding of the relationship between leukemia patients' attitudes toward genetic testing and leukemia-related distress can help optimize clinical implementation of genetic evaluation for HHM.

Methods

Participants and Recruitment

Individuals were eligible to participate if they were at least 18 years old, English-speaking and -reading, and attended at least one appointment at The University of Texas MD Anderson Cancer Center (UTMDACC) on or after March 4, 2016 for a current or previous diagnosis of AML, MDS, acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and/or aplastic anemia (AA). Potential participants were identified through a prospectively-maintained departmental database. Eligible participants' email addresses and primary language were obtained from the electronic medical record. Survey invitations were emailed using an anonymous link through Qualtrics (Qualtrics, Provo, UT). All eligible participants received two invitations: an initial contact email and a reminder email. This study was approved by the UTMDACC Institutional Review Board (IRB).

Procedures and Setting

Data collected through the electronic survey (Supplemental Document I) queried demographic characteristics, patient attitudes, and self-reported distress due to a leukemia diagnosis via the Impact of Event Scale-Revised (IES-R) (Supplemental Document II) [19]. Participants indicated consent by submitting the completed survey. Patient attitudes toward genetic testing were assessed through Likert scale items derived from a pilot study which utilized focus groups of leukemia patients to elicit themes

related to genetic testing [unpublished data]. The survey was piloted among leukemia patients. The IES-R is a well validated and reliable measure of current perceived distress in response to a particular traumatic event. On a scale from 0 (not at all) to 4 (extremely), respondents were asked to indicate how distressing each difficulty had been for them during the past seven days with respect to their diagnosis (Supplemental Document II) [19-23]. Though several researchers have evaluated the IES-R as a screening tool for post-traumatic stress disorder, optimal cut-off values vary considerably between studies and a consensus has not been established [24-28]. Therefore, for this study, the cumulative IES-R score was treated as a continuous variable with higher scores (range 0-88) indicating more distress. Data were collected from November 4, 2019 to January 3, 2020.

Data Analysis

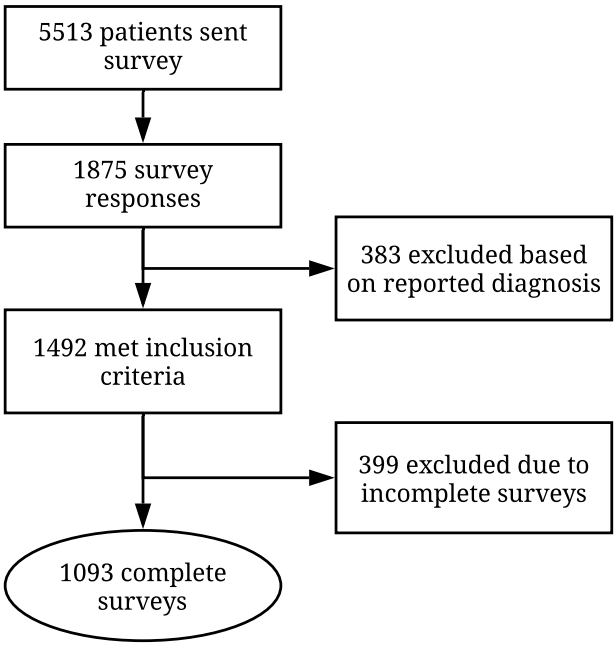
Data were analyzed in Stata (v.13.0, College Station, TX). Descriptive statistics were used for demographics and patient attitudes. Principal component analysis (PCA) was used to analyze the 32-item Likert scale (L1-L32) through dimensional reduction in which highly correlated items are grouped together. Overarching themes were assigned to components with an eigenvalue greater than 1.0. Analysis was focused on themes most relevant to the aims of this study. Likert scale items not accounted for by PCA were assessed individually. Depending on the nature of the data-points in consideration, differences in patient attitudes by demographic factors were assessed by Wilcoxon-Mann-Whitney tests, Kruskal Wallis tests with a *post hoc* Dunn test, or Spearman's correlation. Multivariable analyses were performed to assess the influence of various co-variates on the cumulative IES-R score. Due to its skewed distribution, a zero-inflated negative binomial regression model was fitted for the multivariable analysis. Co-variates were also assessed as possible inflation factors to identify if there were factors that increased or decreased the likelihood of having an IES-R score of zero compared to a higher non-zero value. The final model included covariates deemed to be statistically relevant based on effect measures and 95% confidence intervals (CI), as well as covariates considered to be theoretically relevant based on *a priori* clinical, biological or sociological knowledge. Statistical significance was assumed at $p \leq 0.05$ for quantitative data analyses.

Results

Respondent Demographics

In total, 19.8% (1093/5513) of respondents met inclusion criteria and completed the survey in its entirety (Figure 1).

Figure 1. Eligible Patients and Total Number of Respondents



Demographic data are summarized in Table 1. The median age at the time of the survey was 64 years (range: 21-93 years). The majority of respondents self-identified as male (57%), White/non-Hispanic (88%), with a household income of >$100,000 (58%), a Bachelor's or post-graduate degree (70%), and private or government health insurance (99%). Additional demographics are listed in Supplemental Table I.

Table 1. Respondent Demographics, n = 1093

Age (y)	**Median**	**Range**
	62	21-93
Gender	**n**	**%**
Male	619	56.6
Female	474	43.4
Race/Ethnicity	**n**	**%**
White	959	87.7
Black or African American	19	1.7
Hispanic or Latino	71	6.5
Asian or Pacific Islander	18	1.7
American Indian or Alaskan Native	2	0.2
Multiracial	24	2.2
Income	**n**	**%**
Less than $33,000	84	7.7
$33,000 - $65,999	156	14.3
$66,000 - $99,999	215	19.7
$100,000 - $132,999	195	17.8
$133,000 or more	443	40.5
Education	**n**	**%**
Some high school	3	0.3
High school diploma or GED	77	7.0
Some college	158	14.5
Technical college	33	3.0
Associate's degree	59	5.4
Bachelor's degree	387	35.4
Doctorate or post-graduate degree	376	34.4
Health Insurance	**n**	**%**
No health insurance	9	0.8
Private health insurance	583	53.3
Medicare, Medicaid, or other government	501	45.9
Remission Status	**n**	**%**
Yes	495	45.3
No	377	34.5
Not Sure	221	20.2
Family History of Leukemia	**n**	**%**
Yes	249	22.8
No	756	69.2
Not Sure	88	8.0
Genetic Testing for HHM	**n**	**%**
Yes	45	4.1
No	1,012	92.6
Not Sure	36	3.3

Self-reported leukemia diagnoses of respondents are summarized in Table 2. The majority reported a single diagnosis of chronic leukemia. The combination of MDS and AML was most common amongst those who reported more than one diagnosis of leukemia (13/60, 22%).

Table 2. Respondent-reported Leukemia Diagnoses

Leukemia Diagnosis	**One, n (%)** n = 1033	**Two, n (%)** n = 60	
		First	*Second*
Chronic Leukemia	725 (70)	25 (42)	20 (33)
Acute Leukemia	194 (19)	7 (12)	19 (32)
MDS	105 (10)	22 (37)	16 (27)
AA	9 (1)	2 (3)	1 (2)
Other	-	4 (6)	4 (6)

Chronic leukemia: chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML);
Acute leukemia: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), biphenotypic acute leukemia;
Other: Mantle cell lymphoma, T-cell large granular leukemia, myeloproliferative neoplasm, prolymphocytic leukemia, hairy cell leukemia, NK-cell LGL;
- None reported

Only 11% (122/1093) of respondents reported undergoing HSCT. The majority reported having biological children (83%). A minority reported a family history of leukemia (23%), prior experience with genetic counseling for any reason (9%), or a personal history of genetic testing for HHM (4%). The most commonly reported family history of leukemia was CLL (86/247, 35%) and the majority of respondents with a family history reported only one affected relative (171/247, 69%). Of those who previously underwent genetic testing for HHM, 13% (6/45) reported testing positive for a pathogenic germline mutation associated with an inherited predisposition.

Patient Attitudes

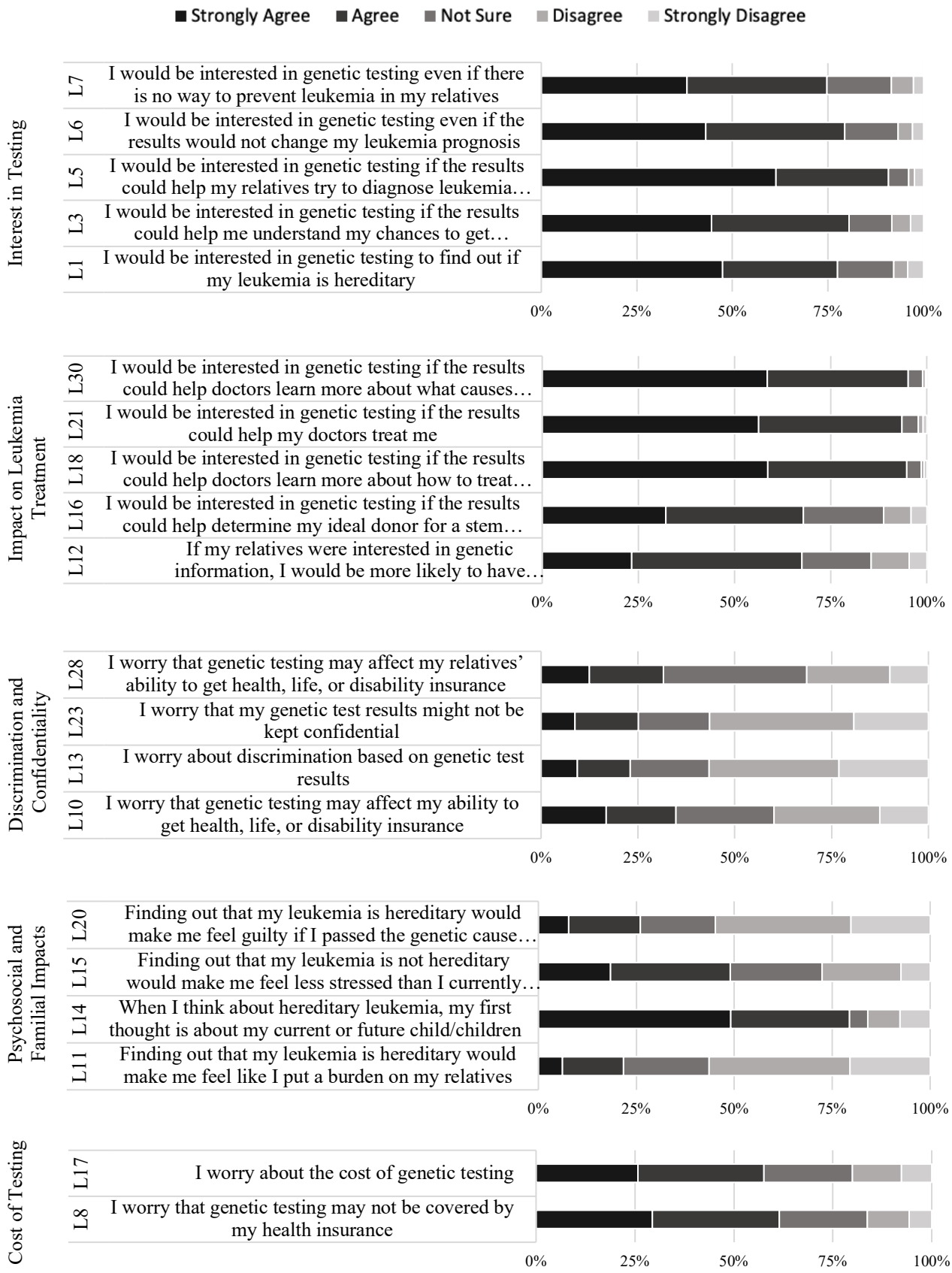
The majority of respondents indicated “agree” or “strongly agree” when asked about their interest in genetic testing to: understand their risk to get another leukemia or cancer (880/1093, 81%), even if it would not change their current leukemia treatment or prognosis (78%; 79%) or prevent leukemia in their relatives (75%), and would choose to undergo genetic testing at the time of this survey (78%). Regarding barriers to genetic testing, slightly more than half of respondents reported “agree” or “strongly agree” to worry about the cost of genetic testing (58%) and/or worry that genetic testing may not be covered by their health insurance (61%). Additional barriers revealed lower frequencies of agreement, specifically, concern about the burden of hereditary leukemia on relatives (22%), impact of genetic testing on health, life or disability insurance for respondents or their relatives, respectively (35%; 32%), confidentiality of genetic test results (25%), and discrimination based on genetic test results

(23%). Furthermore, fewer than 5% (46/1093) of respondents indicated that a skin punch biopsy would prevent them from having genetic testing.

Principle Component Analysis (PCA)

PCA of patient attitudes produced seven components consisting of 23 out of the 32 Likert scale items. The identified themes, in decreasing order of contribution to overall variance, were: 1) interest in genetic testing for HHM, 2) impact on leukemia treatment, 3) discrimination and confidentiality, 4) psychosocial and familial impacts, 5) cost of testing, 6) leukemia attribution to a hereditary cause, and 7) consideration of leukemia cause. The first five themes were most relevant to the aims of the study (Figure 2). Additional themes and nine Likert scale items not accounted for by the PCA are presented in Supplemental Figure I.

Figure 2. PCA Themes



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PCA Themes by Demographics

Several demographic factors were associated with patient attitudes toward genetic testing. Age demonstrated a significant negative association (p <0.05) across all PCA themes: older individuals were more likely than younger individuals to report disagreement to items regarding interest in genetic testing. However, correlation coefficients ranged from -11% to -25% indicating minimal correlation between age and patient attitudes. Additionally, individuals with private health insurance were more likely to report agreement across all PCA themes. Interestingly, patient attitudes toward genetic testing were not significantly associated with remission status nor length of remission. Other significant demographic associations, as identified in univariable analyses, are described per PCA themes 1-5 (Table 3).

1) Interest in genetic testing for HHM – Gender, education level, and family history of leukemia were positively and significantly associated with this component (p <0.05). When evaluating the individual Likert scale items within *interest in genetic testing*, significantly higher scores, indicating more agreement, were reported by women on four of five items (L3, p = 0.006; L5, p = 0.014; L6, p = 0.004; L7, p = 0.013), and those with a family history of leukemia on four of five items (L1, L6, p <0.001; L5, p = 0.018; L7, p = 0.005). There were no significant associations between education level and individual items in this theme.

2) Impact on leukemia treatment – Gender and family history of leukemia were significantly associated with this component (p <0.01). When evaluating the individual Likert scale items within *impact on leukemia treatment*, significantly greater agreement were reported by women on three of five items (L12, L18, p = 0.008; L21, p = 0.009) and those with a family history of leukemia on all five items (L12, p = 0.018; L16, p = 0.014; L18, L21, L30, p <0.001).

3) Discrimination and confidentiality – A statistically significant association was present between ethnicity and this component (p <0.05). When evaluating the individual Likert scale items within *discrimination and confidentiality*, significantly greater agreement was reported by those with Hispanic ethnicity on three of four items (L10, p <0.001; L13, p = 0.001; L28, p = 0.017).

4) Psychosocial and familial impacts – Gender, ethnicity, education level, leukemia diagnosis, and genetic testing for HHM were significantly associated with this component (p <0.05). When

evaluating the individual Likert scale items within *psychosocial and familial impacts*, significantly greater agreement were reported by women on three of four items (L14, $p = 0.010$; L15, L20, $p < 0.001$), those with Hispanic ethnicity on one of four items (L20, $p = 0.009$), some high school or less on two of four items (L15, $p = 0.001$; L20, $p = 0.032$), acute leukemia on two of four items (L14, $p = 0.026$; L20, $p = 0.001$), and genetic testing for HHM on two of four items (L11, $p = 0.015$; L20, $p = 0.001$).

5) Cost of testing – Gender, race/ethnicity, income and education level were significantly associated with this component ($p < 0.001$). When evaluating the individual items within *cost of testing*, significantly more agreement on both Likert scale items were reported by women, those with Hispanic or African American race/ethnicity, a household income of $33,000 or less, and those with some high school or less.

Table 3. Percentage of respondents in each category that reported agreement (agree or strongly agree) to PCA themes 1-5

	Gender †	Race/ Ethnicity †	Income †	Education †	Health Insurance †	Leukemia Diagnosis ††	Fam Hx Leukemia †	Genetic Testing †
Interest in Testing								
L1	NS	NS	NS	NS	74 v 80 **	NS	74 v 88 ***	NS
L3	79 v 83 **	NS	NS	NS	NS	NS	NS	NS
L5	90 v 92 *	NS	NS	NS	78 v 82 **	NS	90 v 93 *	NS
L6	78 v 81 **	NS	NS	NS	NS	NS	76 v 87 ***	NS
L7	73 v 77 *	NS	NS	NS	NS	NS	72 v 84 **	NS
Impact on Leukemia Treatment								
L12	65 v 71**	NS	NS	NS	65 v 69 ***	NS	67 v 72 *	NS
L16	NS	NS	NS	NS	60 v 75 ***	NS	66 v 75 *	NS
L18	94 v 95**	NS	NS	NS	94 v 96 *	NS	94 v 97 ***	NS
L21	93 v 95**	NS	NS	NS	NS	NS	93 v 96 ***	NS
L30	NS	NS	NS	NS	NS	NS	94 v 98 ***	NS
Discrimination and Confidentiality								
L10	NS	33 v 55 ***	NS	NS	23 v 45 ***	NS	NS	NS
L13	NS	22 v 37 **	NS	NS	16 v 28 ***	NS	NS	NS
L23	NS	NS	NS	NS	19 v 30 ***	NS	NS	NS
L28	NS	31 v 39 *	NS	NS	24 v 38 ***	NS	NS	NS
Psychosocial and Familial Impacts								
L11	NS	NS	NS	NS	17 v 26 **	NS	NS	20 v 49 *
L14	78 v 82 *	NS	NS	NS	78 v 80 *	67-70 v 77 *	NS	NS
L15	43 v 57 ***	NS	NS	43 v 60**	45 v 53 *	NS	NS	NS
L20	23 v 30 ***	25 v 42**	NS	26 v 27*	19 v 32 **	24 v 36 **	NS	25 v 56 **
Cost of Testing								
L8	57 v 67 ***	60 v 76 ***	50 v 75 ***	57 v 81 ***	55 v 67 ***	NS	NS	NS
L17	53 v 64 ***	56 v 76 ***	50 v 71 ***	52 v 68 ***	50 v 64 ***	NS	NS	NS

* $p<0.05$; ** $p < 0.01$; *** $p < 0.001$; NS = not significant

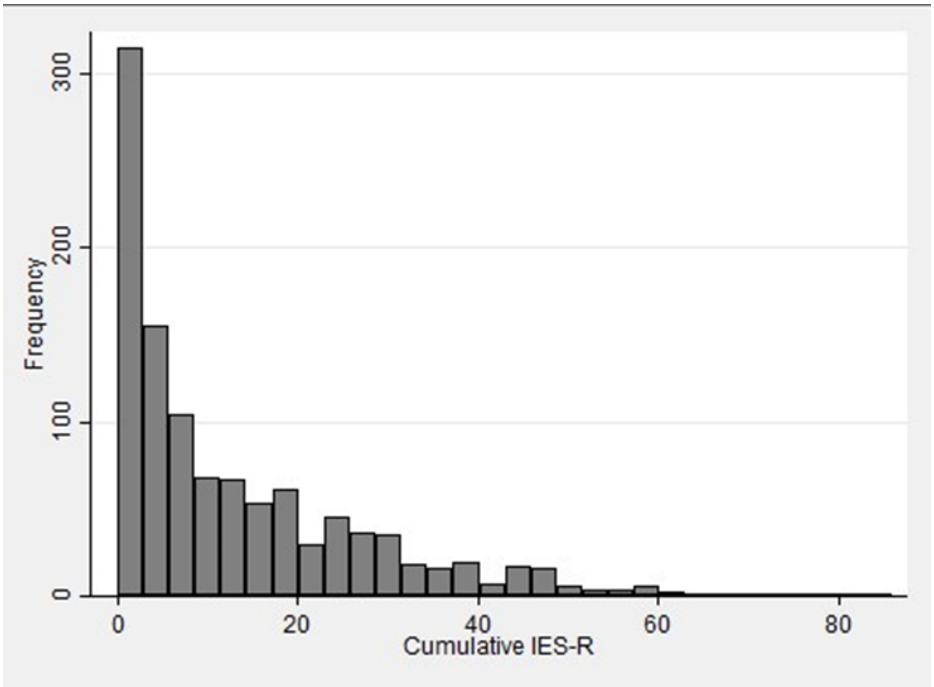
† Gender = male v female; Race/Ethnicity = White/non-Hispanic v Hispanic; Income = $133,000 or more v $33,000 or less; Education = Graduate degree v High school or less; Health insurance = Medicare, Medicaid, or government v Private; Family history of leukemia = no v yes; Genetic testing = no v yes

†† Leukemia Diagnosis = L14) AA-MDS v acute, L20) chronic v acute

Impact of Event Scale-Revised (IES-R)

The median cumulative IES-R score was 7 (range: 0-86; IQR: 20 - 2 = 18) indicating that the majority of respondents report low distress. Furthermore, 18.5% (202/1093) of respondents reported a cumulative score of zero, indicating no distress (Figure 3).

Figure 3. Distribution of Cumulative IES-R Scores



Among individuals who had a cumulative IES-R score greater than zero, significant associations were identified for several covariates (Table 4). Less than 1% (9/1093) of respondents reported having no health insurance and were excluded from the model. Higher levels of agreement with PCA themes 1) interest in genetic testing for HHM and 3) discrimination and confidentiality were associated with an approximately 6% decrease in IES-R scores (risk ratio: 0.94; 95% CI: 0.90, 0.99 and risk ratio: 0.94; 95% CI: 0.89, 0.99, respectively). This contrasts with higher levels of agreement with PCA themes 4) psychosocial and familial impacts, 6) leukemia attribution to a hereditary cause, and 7) consideration of leukemia cause, which are associated with an 11% (risk ratio: 1.11; 95% CI: 1.06, 1.17), 12% (risk ratio: 1.12; 95% CI: 1.05, 1.2), and 24% (risk ratio: 1.24; 95% CI: 1.16, 1.32) adjusted increase in IES-R

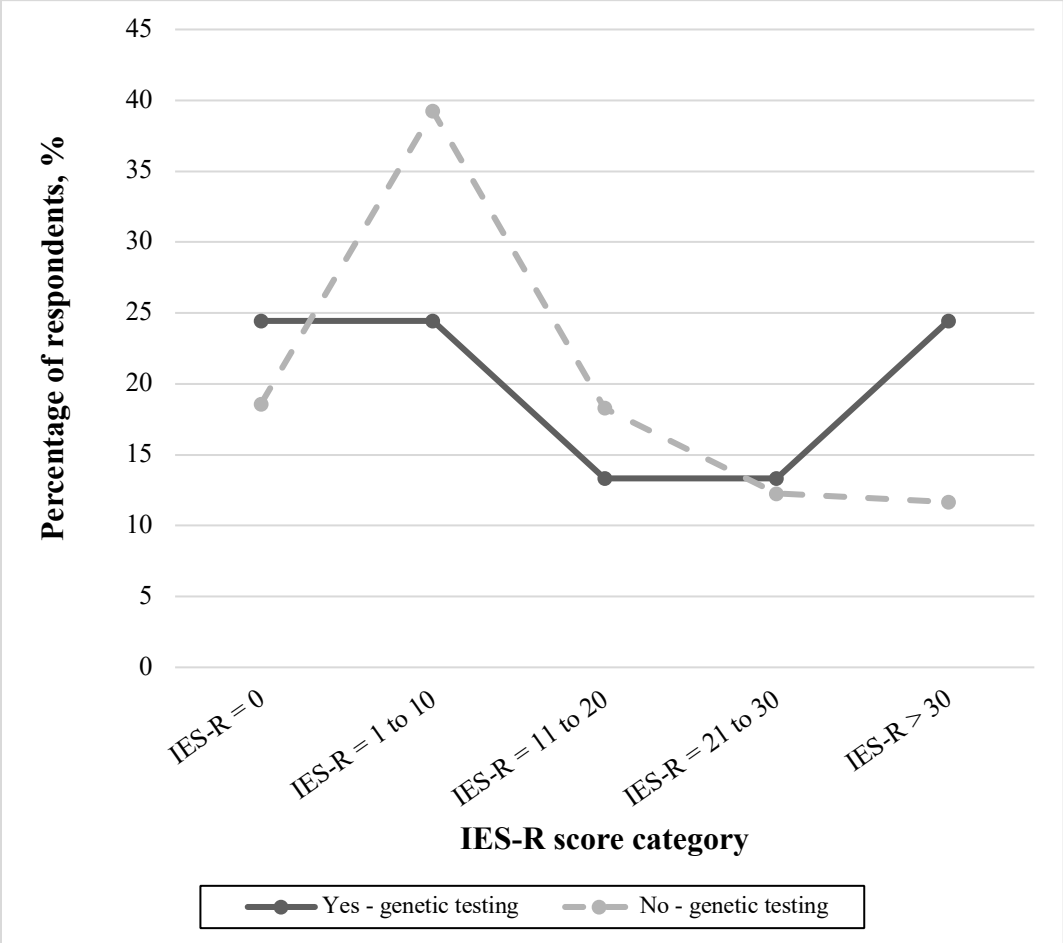
scores, respectively. Additionally, statistically significant and independent decreases in IES-R scores of 10%, 28% and 36% were identified with a 10-year increase in age (risk ratio: 0.90; 95% CI: 0.85, 0.95), remission length of 3 years or more compared to a current leukemia (risk ratio: 0.72; 95% CI: 0.59, 0.88), and no genetic testing for HHM compared to prior testing (risk ratio: 0.64; 95% CI: 0.41, 0.98), respectively. There were no significant associations between IES-R scores and previous experience with a genetic counselor, leukemia diagnosis (chronic vs acute), or interest in pursuing genetic testing for HHM.

Table 4. Risk ratios (with 95% confidence intervals) from zero-inflated negative binomial regression models with cumulative IES-R as the dependent variable

	Sample size	Risk ratio	95% Confidence Interval	p-value
Principal Component Scores				
1) Interest in Genetic Testing for HHM	1084	0.94	0.90 - 0.99	0.017
3) Discrimination and Confidentiality	1084	0.94	0.89 - 0.99	0.037
4) Psychosocial and Familial Impacts	1084	1.11	1.06 - 1.17	<0.001
6) Attribution of Leukemia to a Hereditary Cause	1084	1.12	1.05 - 1.20	0.001
7) Consideration of Leukemia Cause	1084	1.24	1.16 - 1.32	0.001
Age (10-year units)	1084	0.90	0.85 - 0.95	<0.001
Genetic Testing for HHM				
Yes	44	referent		
No	1005	0.64	0.41 - 0.98	0.042
Not Sure	35	0.60	0.34 - 1.04	0.071
Experience with a Genetic Counselor				
Yes	92	referent		
No	992	1.18	0.89 - 1.56	<0.001
Leukemia Diagnosis				
Chronic leukemia	191	referent		
Acute leukemia	721	1.16	0.96 - 1.42	0.130
Myelodysplastic syndrome	195	1.13	0.87 - 1.45	0.361
Aplastic anemia	8	1.76	0.93 - 3.36	0.084
Remission Status and Length				
Current leukemia	375	referent		
Less than 6 months	93	1.01	0.79 - 1.30	0.907
6 months to less than 1 year	73	0.98	0.74 - 1.30	0.890
1 year to less than 3 years	149	1.06	0.85 - 1.32	0.613
3 years or more	173	0.72	0.59 - 0.88	0.002

Inflation factors identified in the analysis that described a higher probability of having a non-zero IES-R score included higher levels of agreement with PCA theme 4) psychosocial and familial impacts, no prior genetic testing for HHM compared to those with a history of genetic testing, and not having children compared to having children. The increased likelihood of either a cumulative IES-R score of zero or a significantly higher non-zero IES-R score among those who reported a history of genetic testing for HHM, is best explained by their bimodal distribution of IES-R scores (Figure 4).

Figure 4. IES-R Score Category by Genetic Testing



Discussion

This study aimed to characterize leukemia patients' attitudes toward genetic testing for HHM, assess motivations and barriers to genetic testing, and elicit current perceived distress due to a leukemia diagnosis. Respondents included a large sampling of the leukemia patient population, however there was an overrepresentation of insured older white males of high education and socioeconomic status with chronic leukemia. Though not generalizable to all leukemia patients, these characteristics are representative of a tertiary referral center patient population.

Overall, the majority of patients indicated positive attitudes toward genetic testing as reflected by high interest in genetic testing for HHM, despite testing not necessarily impacting their own treatment or prognosis and the inability to prevent leukemia in relatives. Patients identified several motivations to seek genetic testing, including to aid their own treatment, contribute to medical knowledge about the etiology and treatment of leukemia, and help relatives try to diagnose leukemia early. These are consistent with previous research in solid tumor patients [13-18]. Interestingly, cost and insurance coverage of testing were the only barriers identified by slightly over half of respondents, despite most reporting they were insured and of relatively high socioeconomic status. This may reflect a lack of knowledge about whether health insurance routinely covers genetic testing and, if not, what it typically costs. Given that this information is often discussed as a part of the genetic counseling process, and it is not otherwise readily accessible, it is reasonable that a population with little experience with genetic counseling would have uncertainty, prompting higher levels of agreement.

An important outcome specific to leukemia patients is the need for a skin punch biopsy to obtain true germline DNA. Skin punch biopsy was not perceived as a barrier to genetic testing. This finding is consistent with results from a previous pilot study [unpublished data]. However, about one third of this study's respondents reported uncertainty about the skin punch biopsy, likely indicating a need for more information about the specifics of the procedure and its safety in patients with leukemia or low blood counts. Education about skin punch biopsy may be especially beneficial for individuals who report less formal education or those from minority race or ethnic groups, as these respondents were more likely to express that a skin punch biopsy may prevent them from pursuing genetic testing.

Women reported more agreement across all themes except discrimination and confidentiality. They were especially more likely to agree with items concerning interest in genetic testing for HHM and the psychosocial and familial impacts of testing. Women's increased interest may indicate that they are naturally more inclined toward genetic testing, whereas men may desire more information about the benefits and limitations of testing before reporting agreement. It is not unexpected that women would report more agreement regarding the psychosocial and familial impacts of testing as women tend to be more emotionally expressive than men due to cultural- and context-dependent gender roles [29-31]. Furthermore, women's historic responsibility as the primary homemakers may contribute to their increased agreement with concern about hereditary leukemia for their current or future children.

Hispanic respondents reported more agreement with items regarding discrimination and confidentiality, the psychosocial and familial impacts of genetic testing, and worry about cost. Hispanics make up the second largest racial/ethnic population in the United States. However, their historic position as an ethnic minority may lead to increased experience with discrimination and explain their concern about the possibility of discrimination based on genetic test results. Hispanics were also more likely to report that they would feel guilty if their leukemia was hereditary and passed on to children. This finding may reflect the Latino culture's values of *personalismo* and *familismo* which stress the importance of interpersonal relationships and central role of family [32]. Hispanic patients undergoing genetic testing for HHM may benefit from focused discussion on the implications for family members and anticipatory guidance surrounding guilt. Increased worry about the cost of testing was reported not only by Hispanics, but also by African American respondents; these groups had the highest proportions of reported household incomes less than $33,000.

Respondents with acute leukemia were more likely to agree with items concerning the psychosocial and familial impacts of testing, specifically that they would feel guilty if hereditary leukemia was passed on to children. The sudden and intensive disease course experienced by patients with acute leukemia, including prolonged hospitalization, frequent infections, intensive chemotherapy and HSCT, may contribute to a strong desire to help others avoid the diagnosis, particularly their children, and lead to more intense feelings of guilt if a leukemia predisposition were passed on.

A significant and unexpected finding of this study is that the vast majority of respondents reported experiencing low distress due to their leukemia diagnosis, despite fewer than half (45%) being in remission. Those who reported prior genetic testing for HHM were more likely to indicate no distress or, if a non-zero IES-R score was reported, higher distress when compared to those without a history of genetic testing. This finding should be interpreted with caution due to the small number of respondents who reported a history of genetic testing (n = 45, 4%). Furthermore, the bimodal distribution observed in these individuals is likely influenced by result type (positive, negative, uncertain); however, a thorough assessment of this hypothesis could not be performed due to the small sample size and lack of variability in the test results (majority reporting negative results). Recency of testing could also not be assessed as information on the timing of tests and subsequent participation in this study was not available. Literature regarding hereditary cancer testing in solid tumor patients has shown that a positive genetic test result can cause increased short-term distress, which diminishes over time [33].

Overall, this study's findings regarding distress seems to be consistent with studies exploring the psychosocial impact of genetic testing in solid tumor populations which suggest that distress is not associated with a cancer diagnosis or genetic testing alone, but better predicted by baseline distress levels and social determinants like interpersonal support systems or socioeconomic resources [34-36]. Several studies have identified elevated cancer-specific distress in individuals who are at increased risk for cancer and referred for genetic testing [37, 38]. Therefore, assessment of distress in unaffected individuals undergoing predictive genetic testing for leukemia predisposition or initial genetic evaluation for a family history of leukemia represents an important direction for future research. Future studies should also use instruments that account for baseline distress levels.

To our knowledge, this is the first large-scale study to characterize leukemia patients' attitudes toward genetic testing for HHM. Despite the large sample size, a limitation of this study is the lack of diversity in respondent demographics. Future studies should assess patient attitudes in minority populations or select for a sample which is more generalizable. This survey was not validated; however, it was developed directly from a pilot study and piloted among leukemia patients. All demographic and disease data were per self-report and not confirmed by medical records or pathology reports. As such,

this study is subject to response bias which could skew towards higher interest in genetic testing. Future studies may benefit from examining attitudes in patients at increased risk to have an underlying HHM, such as those with early-onset myeloid neoplasms or specific molecular mutations suggestive of germline inheritance.

Conclusions

The rapid growth of the field of hereditary hematologic malignancies, and its relative youth in cancer genetics, has likely contributed to lagging clinical implementation of genetic counseling and testing. Furthermore, the often-poor prognosis of an acute leukemia and competing priorities at the time of diagnosis may lead to provider hesitancy to introduce the possibility of HHM and offer referral for genetic evaluation. This large cohort of patients with various diagnoses and stages of disease report low distress as a result of leukemia diagnosis and overwhelming interest in genetic testing, indicating that most leukemia patients are capable of learning about and considering genetic testing for HHM. Barriers prompting concern—cost and insurance coverage of genetic testing—rarely present an issue for the majority of patients in clinical practice and are addressed during genetic counseling. Though distress levels should be assessed on an individual basis, the results of this study suggest that for the majority of individuals, experience with and/or interest in genetic testing are not predictive of higher distress. Therefore, all leukemia patients should be offered the opportunity for genetic counseling and testing when indicated by personal or family history. The results of this study provide valuable insights for delivering the most appropriate care for patients and their families at risk for HHM.

Appendix

Supplemental Document I: Survey

Section A – Demographics

1. Have you previously completed this survey? (Choose one)

   Yes / No

2. What is your current age? _____ years

3. What is your gender identity? (Choose one)
   a. Female
   b. Male
   c. Prefer Not to Answer
   d. Other (please specify):
      _____

4. What is your race/ethnicity? **(Choose all that apply)**
   a. White
   b. Black or African American
   c. Hispanic or Latino
   d. Asian or Pacific Islander
   e. American Indian or Alaskan Native
   f. Other (please specify):
      _____

5. What is your annual household income? (Choose one)
   a. Less than $33,000
   b. $33,000 - $65,999
   c. $66,000 - $99,999
   d. $100,000 - $132,999
   e. $133,000 or more

6. What type of health insurance do you have? (Choose one)
   a. No health insurance
   b. Private health insurance (provided through an employer or purchased myself)
   c. Medicare, Medicaid, or other government health insurance

7. What is your highest level of education? (Choose one)
   a. Some high school
   b. High school diploma or GED
   c. Some college
   d. Technical college
   e. Associate's degree
   f. Bachelor's degree
   g. Doctorate or post-graduate degree

8. Do you have biological children (related by blood)? (Choose one)

   Yes / No

9. Do you have biological siblings (related by blood; both living and/or deceased)? (Choose one)

   Yes / No / Not Sure

Section B – Leukemia History

10. Have you been diagnosed with more than one type of leukemia? (Choose one)

    Yes / No

    If yes, please answer questions 10a-d and then go to question 13. If no, please go to question 11.

    10a. What type of leukemia were you first diagnosed with? (Choose one)
    a. ALL – acute lymphocytic leukemia
    b. AML – acute myelogenous leukemia
    c. MDS – myelodysplastic syndrome
    d. CLL – chronic lymphocytic leukemia
    e. CML – chronic myelogenous leukemia
    f. Aplastic anemia/bone marrow failure
    g. Other (please specify):
       _____

10b. How old were you when you were diagnosed with the first type of leukemia? _____ years

10c. What additional type of leukemia were you diagnosed with? (Choose one)

h. ALL – acute lymphocytic leukemia
i. AML – acute myelogenous leukemia
j. MDS – myelodysplastic syndrome
k. CLL – chronic lymphocytic leukemia
l. CML – chronic myelogenous leukemia
m. Aplastic anemia/bone marrow failure
n. Other (please specify): _____

10d. How old were you when you were diagnosed with the second type of leukemia? _____years

11. What type of leukemia have you been diagnosed with? (Choose one)
    a. ALL – acute lymphocytic leukemia
    b. AML – acute myelogenous leukemia
    c. MDS – myelodysplastic syndrome
    d. CLL – chronic lymphocytic leukemia
    e. CML – chronic myelogenous leukemia
    f. Aplastic anemia/bone marrow failure
    g. Other (please specify): _____

12. How old were you when you were diagnosed with leukemia? _____ years

13. What treatment(s) have you received for your leukemia? **(Choose all that apply)**
    a. No treatment/observation
    b. Blood and/or platelet transfusions
    c. Medications taken by mouth (pill)
    d. Medications or chemotherapy by IV
    e. Stem cell (bone marrow) transplant

14. Have you been diagnosed with another type of cancer(s) before your leukemia (for example, breast cancer)? (Choose one)

    Yes / No

If yes, please answer question 14a. If no, please go to question 15.

14a. How was/were your previous cancer(s) treated? **(Choose all that apply)**
    a. Chemotherapy
    b. Radiation
    c. Surgery
    d. Other (please specify): _____

15. Is your leukemia in remission? (Choose one)

    Yes / No / Not Sure

If yes, please answer question 15a. If no or not sure, please go to question 16.

15a. How long has your leukemia been in remission? (Choose one)
    a. Less than 6 months
    b. 6 months to less than 1 year
    c. 1 year to less than 3 years
    d. 3 years or more

16. Have any of your blood relatives been diagnosed with leukemia? (Choose one)

    Yes / No / Not Sure

If yes, please answer questions 16a and 16b. If no or not sure, please go to question 17.

16a. How many of your blood relatives have been diagnosed with leukemia? _____

16b. What type(s) of leukemia have your blood relative(s) been diagnosed with? **(Choose all that apply)**
    a. ALL – acute lymphocytic leukemia
    b. AML – acute myelogenous leukemia
    c. MDS – myelodysplastic syndrome
    d. CLL – chronic lymphocytic leukemia
    e. CML – chronic myelogenous leukemia

f. Aplastic anemia/bone marrow failure
g. I don't know
h. Other (please specify):
_____

17. Have you ever met with a genetic counselor for any reason? (Choose one)

Yes / No

18. Have you had genetic testing to see if leukemia could run in your family? *This type of genetic testing is different than genetic testing that may have been done on your leukemia to help identify effective treatments. (Choose one)

Yes / No / Not Sure

19. If you have had genetic testing to see if leukemia could run in your family, what was the result? (Choose one)
    a. Positive – gene mutation identified
    b. Negative – no gene mutation identified
    c. Uncertain – inconclusive variant identified
    d. I don't know
    e. I haven't received my results

Section C – Please read the following information before answering the questions in Section D

Several genetic changes (called mutations) have recently been discovered that cause leukemia to run in families. We refer to leukemia that runs in families as "hereditary leukemia." Genetic testing for hereditary leukemia is available and involves looking closely at a person's genes to see if an inherited genetic change caused his or her leukemia. The genetic test requires a procedure to obtain a small piece of skin called a skin punch biopsy. This procedure is safe in patients with low blood counts.

Section D – Please choose the number that best describes how much you agree or disagree with each of the following statements

1 = Strongly Disagree 2 = Disagree 3= Not Sure 4 = Agree 5 = Strongly Agree

		Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree
1	I would be interested in genetic testing to find out if my leukemia is hereditary	1	2	3	4	5
2	Finding out if my leukemia is hereditary would help me make plans for my future	1	2	3	4	5
3	I would be interested in genetic testing if the results could help me understand my chances to get another leukemia or cancer	1	2	3	4	5
4	Finding out that my leukemia is <u>not</u> hereditary would make me feel relieved	1	2	3	4	5
5	I would be interested in genetic testing if the results could help my relatives try to diagnose leukemia early	1	2	3	4	5
6	I would be interested in genetic testing even if the results would <u>not</u> change my leukemia prognosis	1	2	3	4	5
7	I would be interested in genetic testing even if there is no way to prevent leukemia in my relatives	1	2	3	4	5
8	I worry that genetic testing may not be covered by my health insurance	1	2	3	4	5
9	I would be interested in genetic testing to determine if my relatives have a higher chance to develop leukemia	1	2	3	4	5
10	I worry that genetic testing may affect <u>my</u> ability to get health, life, or disability insurance	1	2	3	4	5
11	Finding out that my leukemia is hereditary would make me feel like I put a burden on my relatives	1	2	3	4	5
12	If my relatives were interested in genetic information, I would be more likely to have genetic testing	1	2	3	4	5
13	I worry about discrimination based on genetic test results	1	2	3	4	5
14	When I think about hereditary leukemia, my first thought is about my current or future child/children	1	2	3	4	5

15	Finding out that my leukemia is not hereditary would make me feel less stressed than I currently feel	1	2	3	4	5
16	I would be interested in genetic testing if the results could help determine my ideal donor for a stem cell transplant	1	2	3	4	5
17	I worry about the cost of genetic testing	1	2	3	4	5
18	I would be interested in genetic testing if the results could help doctors learn more about how to treat leukemia more effectively	1	2	3	4	5
19	I think that my leukemia had a hereditary cause	1	2	3	4	5
20	Finding out that my leukemia is hereditary would make me feel guilty if I passed the genetic cause to my current or future child/children	1	2	3	4	5
21	I would be interested in genetic testing if the results could help my doctors treat me	1	2	3	4	5
22	Finding out if my leukemia is hereditary would be good information to share with my relatives	1	2	3	4	5
23	I worry that my genetic test results might not be kept confidential	1	2	3	4	5
24	I would be interested in genetic testing even if the results would not change my leukemia treatment	1	2	3	4	5
25	I often wonder what caused my leukemia	1	2	3	4	5
26	A skin punch biopsy procedure would prevent me from having genetic testing	1	2	3	4	5
27	I think that my environment or chemicals that I was exposed to caused my leukemia	1	2	3	4	5
28	I worry that genetic testing may affect my relatives' ability to get health, life, or disability insurance	1	2	3	4	5
29	Finding out the cause of my leukemia is important to me	1	2	3	4	5
30	I would be interested in genetic testing if the results could help doctors learn more about what causes leukemia	1	2	3	4	5
31	I would choose to have genetic testing to find out if my leukemia is hereditary	1	2	3	4	5
32	I would share my genetic test results with my relatives	1	2	3	4	5

Supplemental Document II: IES-R

IMPACT OF EVENT SCALE-REVISED
Daniel S. Weiss, PhD & Charles R. Marmar, MD

Instructions: Below is a list of difficulties people sometimes have after stressful life events.

Please read each item and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to **leukemia diagnosis**, how much were you distressed or bothered by these difficulties?

Not at all=0, Little bit =1, Moderately=2, Quite a bit = 3, Extremely= 4

Sr.No	Statement	0	1	2	3	4
1	Any reminder brought back feelings about it					
2	I had trouble staying asleep.					
3	Other things kept making me think about it.					
4	I felt irritable and angry.					
5	I avoided letting myself get upset when I thought about it or was reminded of it.					
6	I thought about it when I didn't mean to					
7	I felt as if it hadn't happened or wasn't real					
8	I stayed away from reminders about it.					
9	Pictures about it popped into my mind.					
10	I was jumpy and easily startled.					
11	I tried not to think about it.					
12	I was aware that I still had a lot of feelings about it, but I didn't deal with them.					
13	My feelings about it were kind of numb.					
14	I found myself acting or feeling like I was back at that time.					
15	I had trouble falling asleep.					
16	I had waves of strong feelings about it.					
17	I tried to remove it from my memory.					
18	I had trouble concentrating.					
19	Reminders of it caused me to have physical reactions, such as sweating, trouble breathing.					
20	I had dreams about it.					
21	I felt watchful and on-guard.					
22	I tried not to talk about it.					

Avoidance Subscale = mean of items 5, 7, 8, 11, 12, 13, 17, 22

Intrusion Subscale = mean of items 1, 2, 3, 6, 9, 16, 20

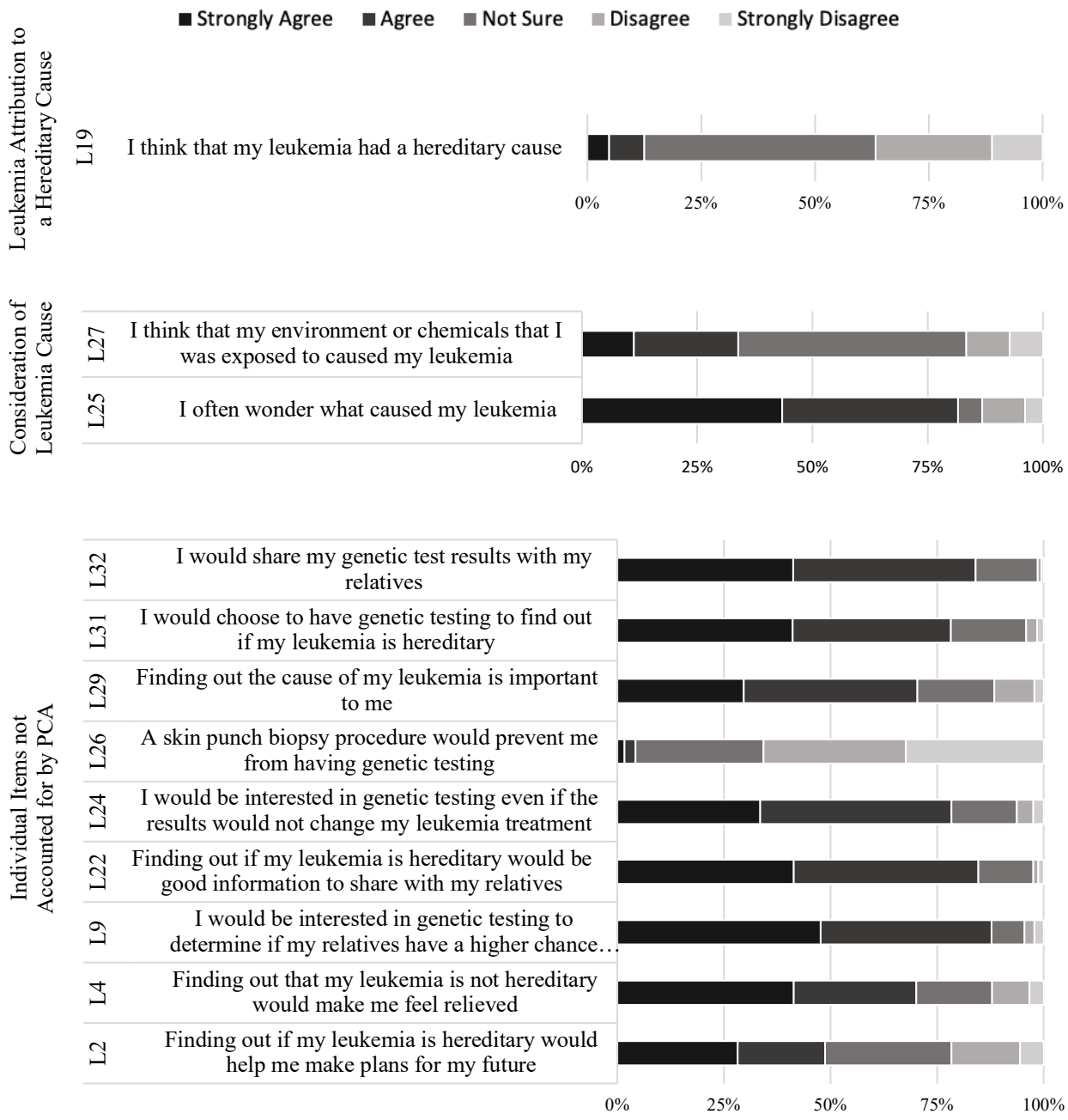
Hyper arousal Subscale = mean of items 4, 10, 14, 15, 18, 19, 21

Note: The IES-R is not a diagnostic or screening tool for PTSD; rather, it relies on a patient's own report of symptoms and is used to gauge response no sooner than two weeks after a traumatic event, as well as to evaluate recovery.

Supplemental Table I: Additional Demographics

Leukemia Type in Affected Family Members	**n**	**%**
ALL	18	7.3
AML	20	8.1
MDS	7	2.8
CLL	86	34.8
CML	8	3.2
AA	1	0.4
Unsure	71	28.8
Other	11	4.5
Multiple	25	10.1
Total	247	100
Amount of Affected Family	**n**	**%**
One	171	69
Two	38	15.4
Three	12	4.9
Four	2	0.8
Five	1	0.5
Six	3	1.2
Eight	1	0.5
Not Sure	19	7.7
Total	247	100
Other Cancer History	**n**	**%**
Yes	224	20.49
No	869	79.51
Total	1093	100
Genetic Counseling for any Reason	**n**	**%**
Yes	96	8.8
No	997	91.2
Total	1093	100
Genetic Testing Results	**n**	**%**
Positive	6	13.6
Negative	26	59.2
Uncertain	3	6.8
I don't know	6	13.6
I haven't received my results	3	6.8
Total	44	100

Supplemental Figure I: PCA Themes 6/7 and Individual Likert scale items



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Vita

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