Title: Illness Representations and Psychological Outcomes in Chronic Lymphocytic Leukemia

Short Title: Illness Representations in CLL

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Abstract

Objectives: Chronic lymphocytic leukemia (CLL) is a lifelong cancer with subtle symptoms. Treatment is not curative and often involves repeated relapses and retreatments. Illness perceptions- cognitive and emotional representations of illness stimuli- were studied in CLL patients to: 1) Identify illness perception "profiles" prior to treatment; and 2) Test if profile membership predicts psychological responses 12 months later as treatment continued.

Design: CLL patients (*N*=259), randomized to one of four cancer treatment trials testing targeted therapy, were assessed before starting treatment and at 12 months.

Methods: The Brief Illness Perception Questionnaire (BIPQ) assessed perceived consequences, timeline, personal/treatment control, identity, comprehension, concern, and emotions toward CLL. Psychological outcomes were depressive symptoms (PHQ-9/BDI-II), negative mood (POMS), and cancer stress (IES-R). Latent profile analysis (LPA) determined number of profiles

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and differential BIPQ items for each profile. Multilevel models tested profiles as predictors of 12-month psychological outcomes.

Results: LPA selected the three-profile model, with profiles revealing Low (*n*=150; 57.9%), Moderate (*n*=21; 8.1%), and High Impact (*n*=88; 34.0%) illness representations. Profiles were defined by differences in consequences, identity, concern, and emotions. Profile membership predicted all psychological outcomes (*p*s<.038). Low Impact profile patients endorsed minimal psychological symptoms; High Impact profile patients reported substantial symptoms.

Conclusions: Results of the first CLL illness representation study provide directions for future clinical efforts. By identifying differences among patients' perceptions of CLL consequences, symptom burden, concerns, and emotional responses, an at-risk patient group might receive tailored psychological treatment. Treatments may address negative perceptions, to reduce psychological risk associated with chronic cancer.

Keywords: illness perceptions, latent profile analysis, chronic lymphocytic leukemia, depression, stress

Data availability statement: The data that support the findings of this study are not available at this time, because the study remains in progress.

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Illness Representations and Psychological Outcomes in Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a cancer involving a neoplasm of B lymphocytes in the peripheral blood, bone marrow, spleen, or lymph nodes. CLL is a lifelong illness. Some new cases are followed for a time ("watchful waiting") until disease indicators are sufficiently elevated to require treatment; other new cases are treated immediately. When treated, now with targeted therapies, symptoms remit for periods ranging from months to years, but relapse is inevitable and treatments not previously used are given (Kaur, 2018). The vagueness of symptoms (e.g., fatigue, swollen lymph nodes) and unpredictable cycling of relapse and retreatment produces uncertainty and worry. Siegel and colleagues (2018) found 27% of patients have clinical depression and 17% have cancer-specific stress, with both associated with higher levels of symptoms, impairments in functional status (Morrison, Flynn, Jones, Byrd, & Andersen, 2016), and stress associated with poor prognosis cell biomarker elevations (Andersen et al., 2018). Although data are few, patients' perceptions of CLL are associated with unique characteristics, such as frequency of treatment cycling (Westbrook et al., 2018).

Broadly, illness perceptions are an individual's own understanding and meaning of an "illness stimulus," such as a symptom (e.g., fatigue), contextual information (e.g., fatigue at the end of the day), or other circumstances providing meaning of the stimulus. Leventhal's Self-Regulatory Model of Illness Behavior (SRM; Leventhal, Meyer, & Nerenz, 1980; Leventhal, Nerenz, & Steele, 1984) begins with the construct of illness stimulus and traces the pathway thereafter, i.e., emotions and thoughts (cognitions) about the stimulus, appraisal, generation of coping strategies, and resultant psychological and illness outcomes. It is a useful paradigm for appreciating how an individual's own emotions and thoughts about their illness may be part of a process leading psychological responses, behaviors, and biological outcomes.

The first step to studying CLL illness stimuli in relationship to outcomes is assessing illness perceptions. Operationalization of Leventhal's cognitive and emotional representation constructs have taken the form of the commonly used Brief Illness Perception Questionnaire (BIPQ; Broadbent, Petrie, Main, & Weinman, 2006). It has six cognitive dimensions (consequences, timeline, personal control, treatment control, identity, and comprehension) and two emotional dimensions (illness concern, emotions; Hagger & Orbell, 2003). Consequences reflects the perception of the illness' impact on one's life. Timeline pertains to the anticipated duration of the illness. Personal control refers to the belief that the individual can control the illness, whereas treatment control refers to the belief treatment can help the illness. Identity refers to the perception that one's symptoms and their severity are a part of the illness. Comprehension pertains to one's understanding of the illness. Concern and emotional representation assess the extent of worry and the extent of negativity about having the illness, respectively.

Investigators using the BIPQ have used either item-by-item analyses (with some examples of summing items) or methods to cluster patients' item responses to study items/patient groups, in order to determine any associations with concurrent psychological responses. Using the item strategy, meta-analyses show higher (more negative) ratings of consequences and identity and either timeline (Hagger & Orbell, 2003) or emotion/concern (Rivera, Corte, DeVon, Collins, & Steffen, 2020) to reliably correlate with negative affect (e.g., stress, depression, anxiety symptoms) across patient types, suggesting the centrality of these particular items for understanding patients' perceptions of illness in general and, by extension, the high likelihood of similar findings for CLL patients. In contrast to these items, comprehension and treatment control are inconsistently correlated with negative affect, and more null relationships than significant ones are found for personal control (Rivera et al., 2020).

With an aim to understand illness perceptions as predictors of outcomes, the cluster strategy has statistical, conceptual, and clinical advantages. With latent profile analysis (LPA), for example, individuals in one cluster report a distinct scoring of the items (a profile or illness representation) that differs from the scoring of the items by another group (Clatworthy, Hankins, Buick, Weinman, & Horne, 2007; McBride, Marlow, Chilcot, Moss-Morris, & Waller, 2021). LPA is often considered a more efficient strategy than analyzing individual items (Magidson & Vermunt, 2004; Norton, Hughes, Chilcot, Sacker, van Os, Young, & Done, 2013), and it

classifies individuals based on similarity of thoughts and emotions about their illness, as represented by item scores. To be theoretically and clinically meaningful, individuals in one group should have different outcomes (e.g., worse stress or depression on follow-up) than individuals in other groups. Such a grouping could be thought of as a marker of vulnerability.

Use of clustering strategies with illness perception data has commonly identified two representations (e.g., "positive" vs. "negative") or three representations ("positive," "negative," and "mixed"), irrespective of the illness/condition studied. As found with item analyses, consequences, identity, and emotions/concern or timeline are the common drivers of cluster distinctions. Thus, individuals with positive representations typically perceive the illness to have few or no severe consequences or symptoms, to last a shorter time, and to be less concerning, compared to those with negative illness representations; individuals in a mixed grouping may endorse moderate values on all items, or a combination of some high and some low item scores. Similar to individual item scores, the valence of the cluster covaries with levels of psychological responses in cross-sectional studies (Lopes, Xavier, Pereira, Stelmach, Fernandes, Harrison, & Carvalho, 2018; McBride et al., 2021; Rivera et al., 2020). More relevant to testing clusters as predictors are the few (4) repeated measures studies of patients with diabetes (Skinner et al., 2011), stroke (Aujla, Walker, Sprigg, & Vedhara, 2018), rheumatoid arthritis (Norton et al., 2013), or breast cancer (McCorry et al., 2013; see online Supplementary Table 1). Across them, consequences, identity, and timeline were the most influential items in determining 2 to 4 clusters and predicting negative psychological responses at intervals ranging from 3 to 12 months.

Studying illness representations of patients with a hematologic malignancy would offer new data for understanding patients with cancer, i.e., one having an atypical presentation requiring coping with a chronic trajectory. Unlike the notable and disruptive signs and symptoms caused by solid tumors (McCorry et al., 2013), those for CLL are subtle and may only be found by chance via laboratory studies done for a routine physical examination, for instance. Whereas the majority of solid tumors have curative treatments, there are no curative treatments for CLL (Rogers et al., 2020; Woyach et al., 2019, 2020). As an immune-related illness, patients with CLL more often die not from the disease but from infections or viruses, as systemic therapies and vaccines are not effective (Siegel et al., 2018). Thus, understanding the illness experiences of

patients with an atypical (i.e., hematologic) cancer would be novel and provide new data regarding a unique chronic illness.

A repeated measures design was used, in which CLL patients were screened, trial-enrolled, and assessed when awaiting that start of a new targeted therapy (ibrutinib). Patients were followed as treatment continued and were reassessed at 12 months, a notable time point because treatment failure is more common prior to 12 months (Parikh, 2018). An LPA was conducted to group patients based on their baseline illness perceptions, with two or three clusters anticipated, considering prior research. The sample included patients receiving their first CLL treatment and patients having experienced one or more treatment relapses; these patients may perceive their illness timeline differently, adding to the robustness of cluster identification. Then, the clusters were tested as predictors of psychological outcomes (depressive symptoms, mood, and stress) at 12 months. Such outcomes are important to patients coping with an unpredictable and lifelong cancer. It was hypothesized that CLL patients with more negative illness representations would report significantly worse depressive symptoms, heightened negative mood, and greater cancer-specific stress.

Methods

Design

Patients with CLL (N=259) were enrolled at a single center in one of four Phase Ib/II trials (ClinicalTrials.gov identifiers NCT01589302 [n=129], NCT02296918 [n=43], NCT02518555 [n=44], and NCT02427451 [n=43]). The trials aimed to determine the clinical efficacy and 2-year progression-free survival of single-agent targeted therapy, the Bruton's tyrosine kinase inhibitor ibrutinib (Rogers et al., 2020; Woyach et al., 2019, 2020). One trial studied ibrutinib only, and the others studied ibrutinib with other therapies (i.e., obinutuzumab, venetoclax, rituximab, vaccinations). All trials included patient-reported outcome (PRO) data collection. See Figure 1 for study flow.

Participants

The mean age of the sample was 62.9 years (SD=10.4), and the majority were male (n=171; 66.0%), Caucasian (n=235; 90.7%), and married/partnered (n=217; 83.8%), with at least some college education (n=181; 69.9%), and an average annual household income between $75,000 and $100,000. Patients new to treatment (first treatment; n=87; 33.6%) and those previously treated (relapsed/refractory; n=172; 66.4%) were studied. For the latter, the average

number of previous treatment regimens was 3.5 (SD=2.6; range 1-13), illustrating the chronicity of the illness.

Procedures

The [BLINDED] Institutional Review Board approved the study and procedures in accordance with its ethical standards and the 1964 Helsinki Declaration. Informed consent was obtained from all participants. Researchers complied with all American Psychological Association ethical standards regarding human subject research participants. Other than prior treatment history, common inclusion/exclusion criteria were used. Eligibility criteria were as follows: physician-confirmed diagnosis of CLL; Eastern Cooperative Oncology Group performance status of 0 (normal activity), 1 (symptoms but ambulatory), or 2 (in bed < 50% of the time); and age 18 years or older. Excluded were patients with systemic, life-threatening medical comorbidities; recent major surgery or medical procedures; active or secondary cancers; or severe psychiatric illness. Ibrutinib is a once-daily, oral therapy (capsule) administered continuously and discontinued when clinical benefit is not maintained. Patients returned to the clinic monthly for drug refills and examinations as needed. The same procedures for data collection were used across trials. At enrollment and 12 months later, patients completed self-report measures (see below). At 12 months, 94.2% of the sample was sufficiently disease-free and continued treatment.

Measures

Illness perceptions. The Brief Illness Perception Questionnaire (BIPQ; Broadbent et al., 2006) was used, consisting of 8 items, one each for the six cognitive perceptions (consequences, timeline, personal control, treatment control, identity, and comprehension) and one each for the two emotional perceptions (concern and emotional representation). A 0- to 10-point scale is used for each item, as recommended (Broadbent et al., 2006, 2015), with higher scores indicating stronger endorsement of the perception.

Outcomes

Depressive symptoms. The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) was used in three trials to evaluate depressive symptoms over the previous two weeks. The PHQ-9 has 9 items scored on a Likert scale from 0 (“not at all”) to 3 (“nearly every day”). The total score can range from 0 to 27, with level classifications as follows: 0-7

(none/mild), 8-14 (moderate), 15-19 (moderate to severe), and 20-27 (severe). Cronbach's alpha at baseline was .80.

The Beck Depression Inventory-2 (BDI-II; Beck, Steer, & Brown, 1996) was used in one trial to evaluate depressive symptoms over the previous two weeks. The BDI-II has 21 items scored from 0 to 3, with higher scores indicating more severe symptoms. The total score can range from 0 to 63, with level classifications as follows: 0-13 (none/minimal), 14-19 (mild), 20-28 (moderate), and 29-63 (severe). Cronbach's alpha at baseline was .90.

Negative mood. The Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1971) measured mood states over the previous week. The POMS is a 65-item measure scored on a Likert scale from 0 ("not at all") to 4 ("extremely"). The total score can range from -32 to 200, with total mood disturbance calculated by summing the Tension, Depression, Anger, Fatigue, and Confusion subscale scores, and subtracting the Vigor subscale score. Level classifications are not used to interpret POMS scores (McNair et al., 1971). The Cronbach's alpha at baseline was .89.

Cancer-specific stress. The Impact of Events Scale-Revised (IES-R; Horowitz, Wilner, & Alvarez, 1979; Weiss & Marmar, 1997) was used to measure intrusive thoughts (e.g., reminders that brought back feelings about having CLL) and avoidant thoughts/behaviors (e.g., "I tried not to talk about CLL") present in the past week. Hyperarousal items (e.g., "I was jumpy and easily startled") were not used (Cella, Mahon, & Donovan, 1990; Golden-Kreutz & Andersen, 2004; Horowitz et al., 1979). Items are scored on a five-point Likert scale from 0 ("not at all") to 4 ("extremely") and summed for a total score ranging from 0 to 64. Cronbach's alpha at baseline was .88.

Covariates

Sociodemographics were obtained and coded: age (years), sex (male/female), race (Caucasian/African American/Latino/Asian American/Native American/other), relationship status (married or partnered/not), education level (coded 1-10 from 8th grade to doctoral degree), and annual household income (coded 1-10 by increments of $15,000 from "less than $15,000" to "more than $250,000"). Other codes were those for clinical trial (4 categories) and prior CLL treatment (yes/no). See Table 1 for demographic and clinical characteristics by trial.

Older age correlates with higher rates of cancer diagnosis, and the probability of developing CLL increases with age (Siegel et al., 2018). CLL is more common in males (1.8%

lifetime prevalence) than females (1.3%), and is most prevalent in Caucasians (Siegel et al., 2018). In cancer, relationship status (partnered) is associated with lower stress, morbidity, and mortality (Ozdemir & Tas Arslan, 2018; Pinquart & Duberstein, 2010). The number of prior treatments reflects disease chronicity and severity.

Analytic Plan

Determination of illness representations. Using Mplus Version 8.2, latent profile analyses (LPA) were performed using participants' baseline illness perceptions. Three different LPAs were run, testing the fit of two, three, and four profiles, consistent with the literature showing two to four illness representations in other samples (e.g., Aujla et al., 2018; McCorry et al., 2013; Norton et al., 2013; Skinner et al., 2011). Typically, LPAs are conducted sequentially, monitoring improvements in model selection criteria until the benefit of adding a profile is exhausted. The Bayesian Information Criterion (BIC; Magidson & Vermunt, 2004; Schwarz, 1978) and the entropy value, each used for model selection for a finite number of models, guide the decision on the number of profiles. The best-fit model has the lowest BIC, an entropy value above 0.8, and a Lo-Mendell-Rubin (LMR) likelihood ratio test p-value below the chosen threshold. The posterior probabilities of profile assignment were extracted for use in the following steps.

To determine the reliability of the profiles, the sample was randomly divided, and an LPA performed with each half. Correlations between the mean values for each BIPQ item of each half were examined, using the Spearman-Brown formula (Rowley, 1978). This formula implements a correction that augments the half-sized sample to a true estimate for the full-sized sample. Additionally, BIPQ item values between profiles were statistically compared to determine if specific items were influential in profile classification.

Illness representations as predictors. Using R version 4.0.5, total scores from the PHQ-9 and BDI-II were computed into Z-scores to create a standardized depression variable. Pearson's correlations (continuous variables), Chi-square tests (categorical variables), and one-way ANOVAs (pairings of continuous and categorical variables) between sociodemographic, treatment, and 12-month psychological variables were inspected. Sociodemographic and treatment variables significantly ($p \leq .10$) associated with the psychological outcome scores were included as covariates in the multilevel models described below.

To test the hypothesis that patients with the most negative illness representation at baseline would experience significantly more severe depressive symptoms, negative mood, and cancer-specific stress 12 months later, analyses were conducted in steps. First, an omnibus test (ANOVA) was performed to test for an overall difference across the groups. Next, a multilevel model was conducted for each outcome, with the profile probabilities (weights), baseline value of the outcome, and Prior Treatment variable as level-one covariates; and a random intercept for trial membership in level two. An alpha level of .05 determined statistically significant results.

Results

Profile Determination

LPAs with two, three, and four profiles yielded BIC values of 9971.298, 9716.983, and 10188.690, respectively (p's for all LMR likelihood ratio tests <.0001), with the three-profile analysis yielding the smallest BIC value. The entropy value for the three-profile analysis was 0.862 (see Supplementary Table 2 for entropy values for each analysis), supporting the conclusion that three latent profiles were most appropriate. The three LPA profiles suggested "Low Impact" (n=150; 57.9%), "Moderate Impact" (n=21; 8.1%), and "High Impact" (n=88; 34.0%) illness representations. Split-half reliability coefficients calculated for each profile's BIPQ means using the Spearman-Brown formula were r=.905 for the Low Impact profile, r=.952 for the Moderate Impact profile, and r=.879 for the High Impact profile. The high intercorrelations demonstrate reliability between the two halves, providing support for the LPA with the full sample.

Table 4 provides demographic and clinical characteristics by profile. Figure 2 depicts the means and variances of each BIPQ item within each profile (shown in tabular format in Supplementary Table 3). As confirmed by contrast analyses (Table 2), four illness perception items -- consequences, identity, illness concern, and emotional representation of the illness -- determined profile membership. Individuals in the Low Impact group perceived their illness as having little impact, few symptoms, and mild emotional influence. Individuals in the Moderate Impact group endorsed modest levels of the four perceptions. Those in the High Impact group expressed strong, negative perceptions of CLL. The profiles were similar in perceptions of illness timeline, personal control, treatment control, and comprehension of CLL. That is, individuals in all three profiles expressed that CLL would last a relatively long time; they have

rather low personal control over its course; the illness is well-controlled by treatment; and they adequately understand CLL.

Profiles as Predictors of Psychological Outcomes

Preliminary analyses. Means and standard deviations of psychological variables at 12 months, cross-tabulated by profile assignment, are provided (Table 3). Overall, symptoms of depression, mood disturbance, and cancer-specific stress were in the mild range. Prior to being transformed into z-scores, mean PHQ-9 scores for the sample at baseline and 12 months were 3.84 and 2.84, respectively; mean BDI-II scores at each time point were 7.27 and 5.13, respectively.

To identify covariates, tests of association between each outcome and potential covariates were conducted (See Supplementary Table 4). Sociodemographic variables were not significantly associated with any 12-month outcome. Mood (POMS) was significantly associated with prior CLL treatment courses [$F(1, 203) = 4.10$, $p=.044$], as was cancer-specific stress (IES) [$F(1, 200) = 7.05$, $p=.009$]. The data suggest that those who had never been previously treated reported more negative mood and cancer-specific stress. Depressive symptoms (PHQ-9/BDI-II) were not significantly associated with any potential covariates.

Primary analyses. After 12 months of continuous treatment, profile assignment predicted all outcomes: depressive symptoms ($F=7.78$, $p<.0001$), negative mood ($F=3.67$, $p=.030$), and cancer-specific stress ($F=3.72$, $p=.028$). Differences were only found for comparison of the High and Low Impact groups. Compared to the High Impact illness perception profile, patients in the Low Impact profile reported significantly fewer depressive symptoms ($p<.001$), no negative mood ($p=.006$) and less cancer-specific stress ($p<.001$) at 12 months. For the Low group, mean scores for each outcome were below the clinical cutoff for mild symptoms. Compared to the Low Impact profile, patients classified in the High Impact profile at baseline endorsed significantly more depressive symptoms ($p<.001$), negative mood ($p=.006$), and cancer-specific stress ($p<.001$) at 12 months. For this group, the mean scores on the depression and negative mood measures were trending toward the clinically elevated range, and the mean stress score was above the threshold designating an 'impact event.' Outcomes for the Moderate profile group were not significantly different from those found in the other two profiles (all $ps>.095$; see Table 3). At 12 months, patients in the Moderate profile group reported moderate levels of depressive symptoms, negative mood, and cancer-specific stress. These effects were found despite

controlling for baseline values of each outcome, trial membership, and relevant covariates (prior CLL treatment for the POMS and IES outcomes).

Discussion

As the first study of illness representations of patients with chronic lymphocytic leukemia (CLL), three unique profiles emerged and predicted differential psychological responses of patients who had been treated continuously for 12 months. LPA identified three profiles (Low, Moderate, and High Impact) differing most notably in perceptions of disease consequences and identity, both seen as cognitive dimensions, and illness concern and emotional representation, regarded as emotional dimensions. Further, profile assignment successfully predicted patients' depressive symptoms, negative mood, and cancer-specific stress at 12 months, with those in the Low Impact profile endorsing minimal psychological symptoms, and those in the High Impact profile reporting the highest psychological symptoms and stress as treatment continued.

It is of note that Leventhal's Self-Regulatory Model of Illness Behavior (SRM) was a conceptualization of illness stimuli, not one of specific illnesses or conditions. Illness perception measures of the late 1990s/early 2000s were mainly an attempt to operationalize SRM constructs of cognitive and emotional representations. The benefit of time and wide usage has found illness perception data across many illnesses and conditions. When the present data are considered in the context of many others, our view is that there are many more similarities across diseases/conditions than there are differences, a relevant observation when considering SRM and related conceptualizations.

Two, three, and four clusters were tested, with the three-cluster model supported by BIC and entropy values. The identification of three profiles is consistent with work by other research teams (Aujla et al., 2018; Berry, Davies, & Dempster, 2017; Graham, Rose, Hankins, Chalder, & Weinman, 2013; Grayson et al., 2013; Harrison, Robertson, Graham, Williams, Steiner, Morgan, & Singh, 2014), although two profiles have been common as well. In LPA, class assignment is based on estimated probabilities, and therefore, measurement error exists within the assigned classes. The sample size of the middle profile (n=21) contrasts sharply to those of the low (n=150) and high (n=88) profiles. Therefore, it is worth considering that the middle profile may be more "noise" (measurement error) than "signal." Relatedly, the item scores for middle group were not found to significantly differ from those of the other groups, with significant contrasts found only for the low and high groups. It is parsimonious to consider the two-class

interpretation rather than the three, and it is also more consistent with CLL's manifestation, i.e., "on" when significant symptoms require treatment, and "off" when symptoms are minimal and no treatment is used.

The items most influential in class determinations were two operationalized as cognitive dimensions - consequences and identity (symptoms) - and two operationalized as emotional dimensions - concern about having the illness and negative emotions arising from it. These items are consistent across a diversity of illnesses/conditions, whether analyzed via single items or clusters. Recognizing and appreciating generalization such as this is important, signaling the relevance of these particular perceptions of illness stimuli, broadly defined. In the case of perceiving CLL, most clearly there were two patient groups: those reporting few symptoms, little concern, and presently viewing CLL as having little consequence for their health, and those reporting significant symptoms, high concern, and presently viewing CLL as most consequential for their health. The lesser support (null effects) for other perceptions, found here and elsewhere, does not suggest they are unimportant, as they may be for particular circumstances, but instead suggests there is insufficient evidence or power for their effects. In this case, the null findings may reflect certain similar perceptions for CLL patients: comprehension (all believed they understood the illness), timeline (all believed CLL would last a long time), and control (most perceived little personal control but greater control by treatment).

The LPA representations predicted all psychological outcomes at 12 months, as CLL treatment continued. To our knowledge, the only cancer study to use clusters as predictors was that by McCorry et al. (2013). Using a sample of 87 women recently diagnosed with breast cancer, two illness representations (negative perceptions and positive perceptions) were identified - defined by consequences, identity, and timeline - and the representations predicted depressive and anxiety symptoms at 6 months. Regarding generality to other repeated measures studies, it was also the case that the same clusters and items predicted depressive and anxiety symptoms at 6 months for patients with rheumatoid arthritis. Other than psychological distress, measures of symptoms or disease markers have not been studied as predicted outcomes; this is an important future direction, as SRM, for example, postulates such importance (Leventhal et al., 1980, 1984).

The clinical relevance of the findings for care of CLL patients is considered. The present data suggest that low scores on the four defining illness perception items could be used as

markers for patients at heightened risk for elevated depressive symptoms or stress. Intervention studies, though few, have been done to "change" negative perceptions using cognitive behavioral therapy, with interventions beginning with an illness perception assessment (see Weldam et al., 2017, for an example with COPD patients, or Siemonsma et al., 2013, for treating individuals with lower back pain). These examples would suggest that efforts to control or reduce troublesome perceptions could be expanded and tested experimentally. Such would allow investigation of whether changing illness perceptions might impact disease-relevant behaviors (e.g., adherence), disease symptoms or outcomes, in addition to psychological responses in accord with the SRM. Intervention steps are important for addressing issues that arise as treatment begins, reducing the likelihood of their continuation with treatment, and possibly preventing reemergence when relapse occurs.

Strengths and limitations of the study are noted. The present research was part of four clinical trials, an important factor in generalizability, as neither the profiles nor the prediction of outcomes was due to trial membership/treatment received or prior treatment history. One trial included "treatment-naïve" patients only, another included relapsed/refractory disease only, and the remaining two had a mix of both. Ibrutinib was a part of all trials, but three of the four included additional novel therapies. LPA is a strategy that has been underutilized in illness perception cluster studies, and these data help to illustrate its utility. The patients in this study came from a large medical center with a comprehensive cancer center. As CLL is a low-incidence disease, it is not unusual for patients to go to larger centers for treatment, rather than remaining in their community. Nevertheless, it would be important to determine if the profile and item findings would generalize to CLL patients treated at other centers. Regarding limitations, patient samples in clinical trials are generally not representative of the population of cancer patients. This sample is representative in terms of sex (disease incidence is higher in men) and race (incidence is highest in non-Hispanic Whites), but not socioeconomic status (Siegel et al., 2018). The sample had a restricted range in both education and income levels, possibly reflective of such individuals having greater resources to travel to a comprehensive cancer center. As noted above, profile analysis uses estimated probabilities, and may exaggerate small differences and/or minimize large differences between individuals; here, this may apply to the Moderate profile.

In summary, LPA analyses identified illness representation clusters for a large CLL sample entering targeted therapy treatment. The representations predicted depressive symptoms,

negative mood, and cancer-specific stress after one year of treatment. By identifying negative representations of illness consequences, symptoms, concerns and emotional responses, an otherwise at-risk patient group could receive tailored illness perception interventions to reduce the likelihood of stress and negative emotions, thus improving patients' long-term cancer experience and quality of life.

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Table 1

Demographic and clinical characteristics of patients by trial

	Trial 1 Ibrutinib only (n=129)	Trial 2 Ibrutinib + obinutuzumab, venetoclax (n=43)	Trial 3 Ibrutinib + vaccines (n=44)	Trial 4 Ibrutinib + obinutuzumab (n=43)
Age (M)	63.8	65.5	60.0	60.7
Sex: male	88 (68.2%)	32 (74.4%)	26 (59.1%)	27 (62.8%)
Race: Caucasian	116 (89.9%)	42 (97.7%)	42 (95.5%)	38 (88.4%)
Marital status: in relationship	107 (82.9%)	11 (25.6%)	6 (13.6%)	8 (18.6%)
Education level*	Bachelor's degree	Bachelor's degree	Bachelor's degree	Associate's degree
Annual income (M)	$75,000-$100,000	$75,000-$100,000	$75,000-$100,000	$75,000-$100,000
Prior CLL treatment: at least 1	129 (100%)	26 (57.8%)	20 (45.5%)	0 (0%)

Note. M: Mean. *: Mode.

Table 2

Significance of contrast analyses between profiles for each BIPQ item (N=259)

Contrast Tests

BIPQ Item	Significance (2-tailed)
Consequences	.029
Timeline	.180
Personal Control	.255
Treatment Control	.099
Identity	.031
Comprehension	.220
Concern	.048
Emotional Representation	.042

Note. Contrast coefficients were -1 for Low Impact illness perception profile, 0 for Moderate Impact profile, and +1 for High Impact profile.

Table 3

Means (M) and standard deviations (SD) of 12-month psychological responses for chronic lymphocytic leukemia patients (N= 259) by profile membership, controlling for baseline scores of the respective outcome,

	M	SD
Depressive symptoms (PHQ-9/BDI-II; Z-scores)		
Low Impact	-0.14	1.06
Moderate Impact	0.07	0.70
High Impact	0.26	0.91
Negative Mood (POMS)		
Low Impact	-4.62	18.06
Moderate Impact	5.17	25.58
High Impact	13.88	30.94

Cancer-Specific Stress (IES)		
Low Impact	4.75	7.64
Moderate Impact	9.01	7.74
High Impact	10.13	10.60

Note. PHQ-9: Patient Health Questionnaire 9-item scale. BDI-II: Beck Depression Inventory-II. POMS: Profile of Mood States. IES: Impact of Events Scale.

Table 4

Demographic and clinical characteristics of patients by latent profile

	Low Impact profile (n=150)	Moderate Impact profile (n=21)	High Impact profile (n=88)
Age (M)	63.6	59.3	62.5
Sex: male	104 (69.3%)	14 (66.7%)	54 (61.4%)
Race: Caucasian	142 (94.7%)	19 (90.5%)	77 (87.5%)
Marital status: in relationship	66 (44.0%)	13 (61.9%)	50 (56.8%)
Education level*	Bachelor's degree	Technical, Vocational, or Certificate program	Bachelor's degree
Annual income (M)	$100,000-$150,000	$75,000-$100,000	$50,000-$75,000
Prior CLL treatment: at least 1	91 (60.7%)	15 (71.4%)	66 (75.0%)

Note. M: Mean. *: Mode.

Figure 1

Study flow diagram

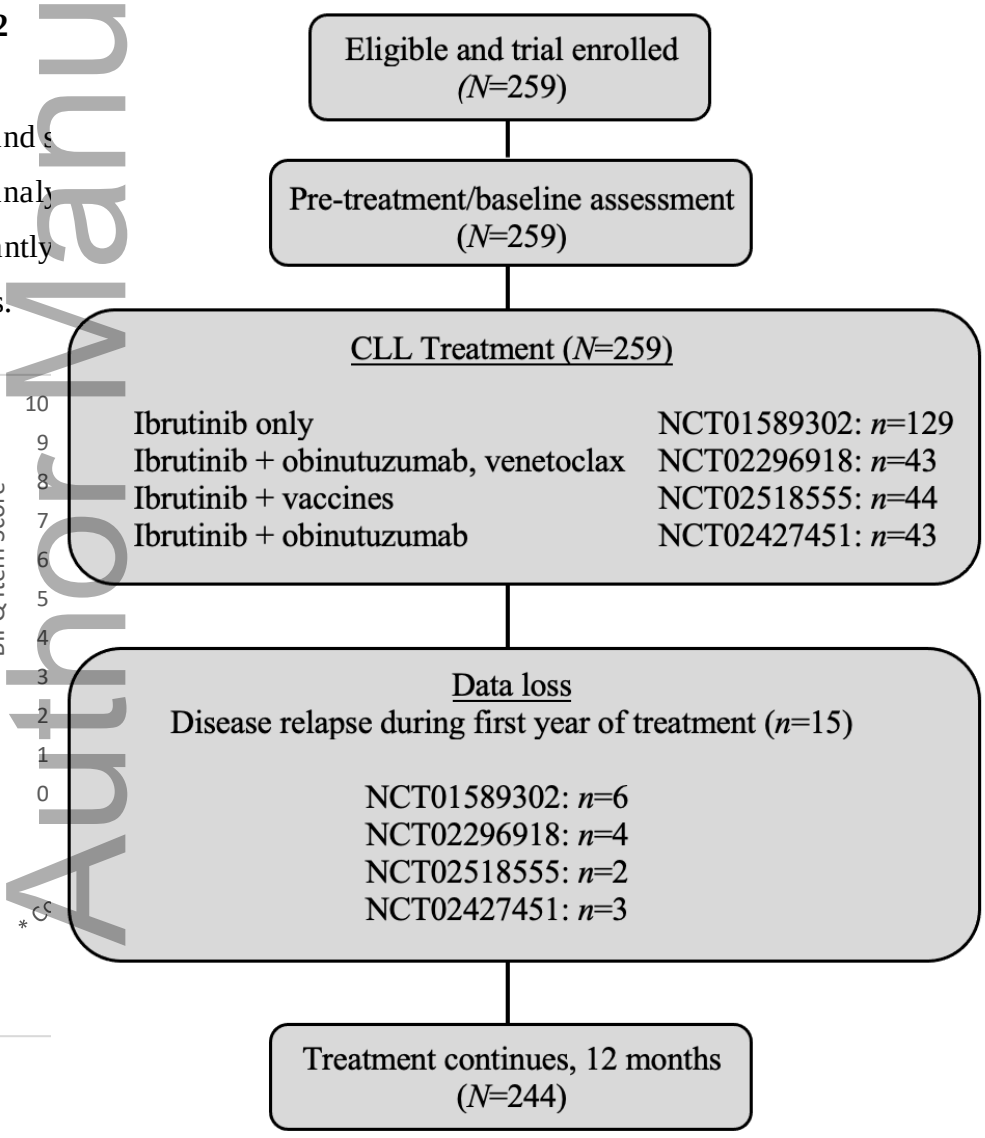

Figure 2

Means and s latent profile analy buted significantly st analyses.