Determinants of Illness Perception in Chronic Lymphocytic Leukemia: Examining the Role of Treatment Phase, Symptoms, and Symptom Change

DISSERTATION

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Abstract

Leventhal's Self-Regulatory Model of Illness Behavior (1980) proposes that, in response to a health-relevant stimulus such as a physical symptom or disease diagnosis, individuals generate a mental representation of the stimulus, or illness perception, which guides coping behaviors and influences psychological and physical health outcomes. Despite extensive research linking illness perceptions to coping and health in several disease groups, lesser attention has focused on better understanding determinants of illness perceptions themselves. The goal of the current project was to test a fundamental postulate of self-regulatory theory, which suggests that illness perceptions are influenced primarily by somatic characteristics of the illness stimulus (e.g., symptom type and severity), prior experiences with the stimulus (e.g., treatment success or failure), and changes in the stimulus over time. To do so, two studies were conducted, both in samples of patients with chronic lymphocytic leukemia (CLL). Using a cross-sectional design, Study 1 contrasted illness perceptions among CLL patients (N=330) from three groups differing in symptom severity and prior CLL experiences: active surveillance (n=100), initiating a first treatment (n=78), and initiating treatment for relapsed/refractory disease (n=152). Analysis of variance revealed that, while consequences, identity (symptoms), and illness concern were poorer among patients at each successive phase of treatment, perceptions of how well one understands CLL (coherence) and how long CLL will last (timeline) were poorest among those earliest in the trajectory (i.e., active

surveillance). Patients initiating a first treatment believed most strongly that they could personally control CLL (personal control) and that treatment would be helpful (treatment control). Study 2, using a longitudinal, single group design, examined specifically the role of somatic stimulus severity among relapsed/refractory CLL patients (N=152) initiating treatment with targeted therapy (i.e., ibrutinib). Using both subjective (i.e., self-reported fatigue), and objective (i.e., hemoglobin, lymph node volume, organ enlargement, lymphocyte count) measurements of somatic stimulus severity, several relationships consistent with self-regulatory theory emerged. First, both subjective fatigue and objective disease markers covaried with illness perceptions at pre-treatment, and the majority of illness perceptions improved over the first 2- and 5-months of treatment when rapid changes to illness stimuli were occurring. Moreover, multiple regression analyses indicated that, controlling for number of prior CLL therapies, changes in subjective and objective stimuli which occurred during the first 2- and 5-months of treatment accounted for significant portions of variance in illness perception change. Cumulatively, results provide novel confirmatory support for Leventhal's postulate that symptoms and disease experiences are central factors in the development of illness perceptions. Implications for theory and research are discussed.

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Fields of Study

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Chapter 1: Introduction

A goal of clinical health psychology is to understand the determinants of health-related behavior and develop interventions for promotion of health and quality of life. In pursuit of this endeavor, theoretical models have been developed, each varying in emphasis, empirical support, and clinical utility. One validated model is Leventhal's Self-Regulatory Model of Illness Behavior (SRM; Leventhal, Meyer, & Nerenz, 1980), which highlights mental representations of health threats as central to how individuals understand and cope with disease. These mental representations of health threats, or illness perceptions, are rapidly generated in response to illness stimuli such as diagnostic information or physical symptoms, and predict psychological, behavioral, and physical outcomes across a number of health conditions (For meta-analytic reviews see: (Broadbent et al., 2015; Dempster, Howell, & McCorry, 2015; Hagger & Orbell, 2003; McSharry, Moss-Morris, & Kendrick, 2011; E. Richardson, Schüz, Sanderson, Scott, & Schüz, 2016).

Despite evidence linking illness perceptions to health and coping in several disease groups, less is known about *determinants* of illness perceptions (Leventhal, Phillips, & Burns, 2016; Lowe & Norman, 2017). According to theory, illness perceptions are formed from multiple sources including symptom experiences (i.e., type and severity), and previous experiences with the stimulus (e.g., treatment). Illness

perceptions are also theorized to change as experiences with the stimulus are acquired and changes in the stimulus occur (Leventhal, Nerenz, & Steele, 1984). These theoretical postulates, however, have received little research attention, providing a rich opportunity for growth in the illness perception literature.

Thus, the major objective of this project was to examine how illness experience, symptoms, and symptom change impact illness perceptions. In furtherance of this objective, two studies were conducted among patients with chronic lymphocytic leukemia (CLL). CLL is a relevant paradigm for these tests. The disease trajectory is unique, having three distinct phases: indolent disease requiring no treatment (active surveillance), active disease requiring treatment initiation, and relapsed and refractory disease. The CLL "illness stimulus" varies between these groups in meaningful ways, including symptoms (both type and severity), and previous experiences with CLL – both of which are theorized as central determinants of illness perception.

Two studies were conducted. Study 1 tested whether illness perceptions varied as a function of the symptoms and illness experience of CLL through comparison of the three groups. Study 2 examined how illness perceptions changed vis-a-vis illness stimulus change occurring with treatment. In the sections that follow, Leventhal's SRM will be introduced and literature regarding the development and assessment of illness perceptions will be reviewed. Following this, determinants of illness perception will be described, with an emphasis on literature documenting the influence of treatment phase, symptoms, and symptom change. After this, a description of chronic lymphocytic leukemia will be provided, and the specific aims and hypotheses for the project will be outlined.

Self-Regulatory Model of Illness Behavior

Self-regulatory theory is based in the conceptualization of human cognition and behavior as inherently purposeful and goal directed (Anderson, 1983; Leventhal, Brissette, & Leventhal, 2003; Newell, 1980). It proposes that humans are active problem solvers who identify discrepancies between a current state (e.g., illness) and a goal state (e.g., health), and implement strategies to reduce or resolve this discrepancy. Leventhal's Self-Regulatory Model of Illness Behavior (SRM; Figure 1) stems from self-regulatory theory, and describes how individuals respond to health threats and make attempts to resolve or reduce them. The model begins with the notion of an illness stimulus, which Leventhal defined as "somatic stimuli and general information about the disease threat" (pp. 380, Brownlee, Leventhal, & Leventhal, 2000; Diefenbach & Leventhal, 1996; Leventhal, Leventhal, & Contrada, 1998). Leventhal and colleagues use "stimulus" and "threat" interchangeably, and typically refer to the stimulus as the specific illness (e.g., "a cold") if it is known. Examples of illness stimuli therefore include an ache or pain, a heart palpitation, abnormal lab results, or receipt of a specific diagnosis (e.g., "cancer"). Leventhal and colleagues have also characterized external information such as the occurrence of disease in a close family member or friend as an illness stimulus (Diefenbach & Leventhal, 1996).

The SRM suggests that, upon experiencing an illness stimulus or health threat, individuals create a mental representation of the stimulus in order to "make sense" of and cope with (i.e., regulate) the experience (Hagger & Orbell, 2003). These mental representations of the stimulus are referred to as illness perceptions, though additional

terms have been used (e.g., illness representations, illness cognitions). The content of one's illness perception is informed predominantly by the *type and severity* of somatic experiences associated with the stimulus, as well as personal *previous experiences* with the stimulus (Diefenbach & Leventhal, 1996; Leventhal et al., 1980, 1984). Furthermore, illness perceptions are theorized to "update" over time as symptoms change, new knowledge is acquired, and efforts to control or cure the disease succeed or fail. For example, one's mental representation of mild abdominal pain would theoretically differ extensively from that of severe abdominal pain on several dimensions, including how concerning the threat is, what the potential consequences are, and how controllable it is appraised to be. Similarly, someone who has accumulated several experiences with severe abdominal pain, perhaps receiving a specific diagnosis and experiential knowledge that resting will allow the symptom to dissipate quickly, will, theoretically, construct a different representation than someone experiencing the stimulus for the first time.

Leventhal and colleagues have called for more thorough examination of determinants of illness perceptions in recent reviews (Leventhal, Leventhal, & Breland, 2011; Leventhal et al., 2016). While understanding illness perceptions as predictors of coping and outcomes has been (and remains) an important research agenda with potential for clinical utility, authors propose that a critical gap exists regarding the "dynamic mechanisms underlying these predictions" (Leventhal et al., 2016; pp. 936), including how illness perceptions are generated and how they interact with other factors (e.g., the stimulus) over time. Addressing these gaps would not only verify fundamental theoretical postulates of the SRM, but also foster a more nuanced understanding of health behavior necessary to optimize intervention development.

Cognitive and Emotional Representations of the Illness Stimulus

Research has identified several dimensions of illness perceptions (Baumann & Leventhal, 1985; Broadbent, Petrie, Main, & Weinman, 2006; Lau & Hartman, 1983; Moss-Morris et al., 2002). *Identity* reflects one's label for the stimulus and the symptoms they perceive as belonging to it (e.g., nausea, pain, malaise). The *consequences* dimension refers to beliefs about the impact of the stimulus on overall quality of life or how it may affect functional capacity (Hagger & Orbell, 2003). Perceptions of disease controllability reflect the belief that the stimulus can be controlled by the self (*personal control)* and/or expert intervention (*treatment control)* (Scharloo & Kaptein, 1997). The *timeline* dimension represents patients' appraisal of the stimulus and/or its symptoms as acute, chronic, or cyclical. The *cause* dimension represents beliefs about etiology, whether biological (e.g., genetics, germs; Heijmans, 1998), behavioral (e.g., smoking, diet; Diefenbach & Leventhal, 1996), or psychological (e.g., stress, depression; Moss-Morris et al., 2002).

The above dimensions are collectively known as "cognitive" representations of the illness stimulus (Leventhal et al., 1984), as they are thoughts and beliefs. The SRM also proposes that emotions occur in tandem with cognitive representations (Figure 1). These rapidly generated emotional responses associated with the stimulus are collectively known as *emotional representation* (Moss-Morris et al., 2002). For example, an individual who experiences chest pain after strength training who attributes the sensation to muscle soreness and perceives the symptom as controllable with few consequences will theoretically experience less anxiety than if the stimulus was appraised as indicative

of a heart attack. Similarly, a woman who discovers a lump during a routine breast self-exam may immediately experience fear if the stimulus is appraised as indicative of breast cancer.

Assessment of Illness Perceptions

Early studies used open-ended interviews to assess illness perceptions (Baumann & Leventhal, 1985; Lau, Bernard, & Hartman, 1989; Lau & Hartman, 1983; Leventhal et al., 1980; Meyer, Leventhal, & Gutmann, 1985). In them, patients were asked specific questions such as "In your own words, what do you think high blood pressure means?;" "Do you think you can tell when your blood pressure is up? How can you tell?;" "How long do you think you'll need to be on treatment?" Growing interest in illness perceptions spurred development of the 38-item Illness Perception Questionnaire (IPQ; Weinman, Petrie, Moss-Morris, & Horne, 1996), which measured five cognitive dimensions of illness perception (consequences, identity, timeline, controllability, cause). This questionnaire was later revised (IPQ-Revised; Moss-Morris et al., 2002) in several ways. First, factor analyses revealed that controllability was better represented by two separate factors: personal control and treatment control. Items were also added to assess cyclical timeline beliefs (e.g., "The symptoms of my illness change a great deal from day to day;" "My symptoms come and go in cycles") rather than the previous acute/chronic distinction. Emotional responses (a dimension of emotional representation) and illness coherence scales were also added. Illness coherence was proposed as a meta-cognitive component of illness perception reflecting the extent to which individuals believe they understood their illness (Moss-Morris et al., 2002).

A brief version of the IPQ-Revised was then developed (BIPQ; Broadbent et al., 2006; Appendix D), which assesses each illness perception dimension using a single item. With this version, an "illness concern" item was added under the umbrella of emotional representation which captured the extent to which individuals were concerned about their illness. Thus, the BIPQ possesses six items that assess cognitive representations (i.e., consequences, identity, timeline, personal control, treatment control, coherence), and two that assess emotional representation (i.e., emotional responses and concern). For the BIPQ, a single sum composite score reflecting "total illness threat" can be calculated, which indicates the extent to which patients have a more negative overall perception of their illness.

Determinants of Illness Perceptions

Although several meta-analytic reviews have linked illness perceptions to mental and physical health outcomes in patients with chronic illness (Broadbent et al., 2015; Dempster et al., 2015; Hagger & Orbell, 2003; McSharry et al., 2011; E. Richardson et al., 2016), fewer studies have examined the relationship between illness stimuli and subsequent perceptions. Consistent with self-regulatory theory, the few available studies center around the role of symptoms, their severity, and change (or lack thereof) over time. The literature reviewed below first summarizes results of studies which operationalize illness stimuli through study of patients at different phases or stages of the same disease. Then, cross-sectional and longitudinal studies which examine the impact of symptom severity and its change on illness perception are reviewed.

Stage/Treatment Phase as the Illness Stimulus

Stages of disease summarize important differences in symptoms and treatment needs among patients with chronic illness. Two studies which compare illness perceptions between patients at different stages of the same disease are available for review. Jansen and colleagues (2013) compared illness perceptions between pre-dialysis chronic kidney disease patients (CKD; N=266) managed with pharmacotherapy (Stage 4; n=105) and those on dialysis (Stage 5; n=161). CKD is a relevant comparison group to CLL – both diseases are incurable, and early stage patients in both groups are typically asymptomatic. Further, treatment protocols at later phases of CKD (e.g., dialysis) are associated with greater risk for toxicities, as also observed in CLL. Study results indicated that patients on dialysis perceived more consequences believed more strongly that treatment would be helpful (i.e., treatment control) than did pre-dialysis patients. Perceptions of the illness timeline, personal control, coherence (i.e., illness understanding), and emotional responses did not differ between groups. Illness identity (i.e., symptoms) was not examined. In follow-up analyses, coherence was shown to have a parabolic relationship with time (0 to 10 years), increasing through approximately 5 years on dialysis and declining thereafter. Pagels and colleagues (2015) also studied CKD treatment stage (stages 2-3[n=35] vs. 4-5[n=19]). Later stage CKD patients perceived more symptoms (identity), consequences, and experienced more negative emotions in response to CKD (emotional responses). Coherence, timeline, and personal control did not differ between groups. Treatment control was not examined.

The findings of these studies are in partial agreement with self-regulatory theory. Consequences and identity were higher among later stage patients, an expected

relationship considering the increased symptoms, functional limitations, and treatment burden associated with later stage CKD. Results also suggested a trend towards increased illness coherence among later stage patients or those with longer time on treatment, supporting the hypothesis that illness coherence increases as experience with the disease is acquired. Later stage CKD patients reported higher treatment control perceptions relative to earlier stage patients, potentially indicating that dialysis treatment is appraised as more effective in controlling CKD than pharmacotherapy. Personal control and timeline did not vary between groups, which may be a result of the chronic/incurable nature of CKD. Lack of group differences in emotional responses observed by Jansen and colleagues is unexpected, but could indicate that emotional responses among stage 4 and 5 patients are similar to each other yet dissimilar to earlier stages. This would explain the significant group differences in emotional responses in Pagels and colleague's comparison of stages 4 and 5 vs. stages 2 and 3.

Considering the context of CLL, these studies would suggest that consequences and identity may be higher among patients at later phases of treatment with greater symptom severity. Coherence, too, may increase across the CLL treatment trajectory as experience with the disease is acquired. The pattern of elevated treatment control beliefs observed among stage 5 CKD patients relative to stage 4 may reflect greater confidence in more aggressive treatment approaches. If this relationship were to replicate in CLL, we would expect higher treatment control beliefs among patients at each successive phase of CLL treatment. Negative emotional responses were also found to covary with later stage CKD when compared to earlier stages. If this is indeed related to increased symptom severity at later stages of treatment, one would anticipate a replication of this

finding in CLL. Lastly, CKD treatment groups did not differ on timeline and personal control, potentially because the disease has a fixed timeline (incurable), and as a result, patients cannot facilitate curing the disease. If this pattern were to extend to CLL, we would expect that timeline and personal control would not vary between CLL treatment groups.

Symptoms/Symptom Severity as the Illness Stimulus

Cross-Sectional (Supplementary Table 1)

Self-regulatory theory suggests that symptoms and their severity are primary determinants of illness perceptions (Leventhal et al., 1980, 1984). As such, most studies examining determinants of illness perception have focused on symptom/disease severity. However, the available literature is limited in its assessment of severity, frequently relying on self-report. Objective measures of disease severity are potentially more useful as emotions may influence both symptom and illness perception reporting (Aronson, Barrett, & Quigley, 2006).

Chisari and Chilcot (2017) studied illness perceptions in vulvodynia (chronic vulvar pain) patients (N=335) using an online cross-sectional survey design. Greater self-reported pain severity was associated with more negative perceptions of identity, consequences, personal control, treatment control, coherence, and emotional responses. Timeline was not associated with symptom severity; concern was not examined. Significant cross-sectional relationships between greater self-reported symptom severity and more negative illness perceptions have been documented in other samples, including those with breast cancer (Leonhart et al., 2017), osteoarthritis (Knowles et al., 2016),

chronic pain (Costa, Vale, Sobral, & Graca Pereira, 2016), inflammatory bowel disease (Artom, Czuber-Dochan, Sturt, Murrells, & Norton, 2017; De Gucht, 2015; Knowles, Cook, & Tribbick, 2013), chronic overactive bladder (Pretorius et al., 2014), Chrohn's disease (Zhang et al., 2016), psoriasis (Nordbø, Aamodt, & Ihlebæk, 2017), and chronic kidney disease (Chilcot et al., 2016).

Only three studies, to our knowledge, have related objective markers of symptom severity to illness perceptions, with none utilizing an oncology sample or longitudinal design. Studying patients (N=142) with osteoarthritis, Dalbeth and colleagues (2011) observed that greater objective symptom severity (e.g., serum urate, flare frequency) predicted poorer scores on consequences, identity, personal control, treatment control, and emotional responses. Timeline and coherence were unrelated to symptom severity, and concern was related to subjective severity only. In another study of arthritis patients, Edelstein and colleagues (2012; N=202) observed that a higher number of fractures covaried with poorer scores on consequences, identity, controllability, and emotional responses. Timeline was unrelated to number of fractures; coherence and concern were not examined.

Lastly, in a study of illness perceptions among cardiovascular disease patients (N=75), Greco and colleagues (2015) used left ventricular ejection fraction as a measure of disease severity. Authors found that ejection fraction predicted a more negative perception of cardiovascular disease (using the total illness threat score) and that illness perceptions mediated the relationship between objective severity and health satisfaction.

Change in the Illness Stimulus (Supplementary Table 2)

Another central hypothesis of the SRM is that illness perceptions are "updated" as new knowledge and experiences with the stimulus are acquired and changes in the stimulus occur. Foster and colleagues (2008) provide support for this hypothesis in their examination of changes in disability over 6 months in 1,591 patients with lower back pain. Patients with improvements in self-reported pain scores over the 6-month period reported reduced consequences, fewer symptoms (identity), and more favorable scores on personal control, treatment control, and emotional responses. Timeline and coherence did not change with symptom improvements; illness concern was not evaluated.

Although Foster and colleagues (2008, above) examined the relationship between illness stimuli and perceptions quantitatively, most longitudinal studies examine changes in illness perceptions (e.g., pre/post differences, repeated measures analyses) in samples of patients with presumed illness stimulus change (e.g., those receiving a treatment) or instead, monitor patients for any illness perception change that might occur. As an example of the first case, Astin and colleagues (2006) studied coronary heart disease patients (N=117) receiving transluminal coronary angioplasty. Illness perceptions were rated prior to the procedure and again 6-8 months later. As would be expected among patients with improving symptoms, consequences and identity were improved at follow-up. Interestingly, personal and treatment control beliefs were lower at follow-up. Timeline perceptions became more chronic, potentially reflecting patients' learning over time that the treatment would not cure the disease. Emotional responses, concern, and coherence were not examined.

As another example of changes in illness perception among patients with presumed stimulus changes, Janssen and colleagues (2013) studied a mixed sample of cardiac patients (N=158) pre and post completion of a 3-month outpatient cardiac rehabilitation program. At follow-up, patients reported more favorable scores for consequences, identity, treatment control, coherence, and emotional responses. Only timeline and personal control dimensions were unchanged. These findings are largely expected, but an argument could be made that personal control should increase as patients learn new ways to manage health during rehabilitation. Fischer and colleagues (2010) indeed observed pre/post improvements in personal control among chronic obstructive pulmonary disease (COPD) patients attending cardiac rehabilitation. As no COPD patients were included in the Janssen et al. report, these differential findings may reflect disease-specific differences.

Another subgroup of longitudinal studies monitors illness perceptions over time, with no presumption of changes in the stimulus. Although patients are not undergoing an acute period of symptom change as would be experienced during treatment, they inform our understanding of the "experiential" component of the illness stimulus – that is, the possibility that acquired experiences (e.g., doctors' visits, living daily with the condition) impact illness perception in addition to symptom change. For example, Bijsterbosh and colleagues (2009) studied 241 patients with osteoarthritis completing a 6-year follow-up. Compared to baseline scores, patients at follow-up reported improvements in both coherence and emotional responses. Further, patients grew to perceive their disease as more chronic and less personally controllable. Identity, consequences, and treatment control did not change. Although changes in pain or disability were not reported, this

pattern of illness perception change would be expected among patients with stable symptoms learning to live with the condition over time.

Tasmoc and colleagues (2013) studied clinically stable hemodialysis patients (N=81) with end stage kidney disease over 6-years. Although identity scores did not change over time, patients reported fewer consequences, enhanced helpfulness of treatment, a better understanding of their illness, and reduced emotional responses. This pattern of improvement is consistent with successful management of stable disease. Timeline perceptions became more chronic and personal control did not change.

Lawson and colleagues (2008) examined illness perception change over 2 years in 158 clinically stable patients with diabetes. Again, illness coherence and emotional responses improved with time. Identity, consequences, timeline, personal control, and treatment control remained stable over the follow-up period.

Dempster and colleagues (2011) examined 12-month change in illness perceptions among 189 esophageal cancer survivors (assessed twice). On average, patients were 4-years post-treatment. Patients demonstrated improvements in perceived consequences and identity, and, interestingly, decreases in treatment control. Timeline, personal control, and coherence remained stable; emotional responses and concern were not examined.

Lastly, Rutter & Rutter (2007) assessed illness perceptions of irritable bowel syndrome patients (N=42) at three occasions over 12-months. The authors observed no changes in any dimension examined (i.e., identity, consequences, timeline, controllability), attributing stability to minimal changes in treatment or clinical state of the patient sample over the 12-month interval. Although health status of patients was not

assessed, these findings would be expected in a sample of patients with symptomatic, but stable disease.

In combination, studies suggest several patterns of illness perception change. Most consistently, patients with observed or presumed symptom improvements displayed favorable changes in consequences, identity, and emotional responses (Astin & Jones, 2006; Foster et al., 2008; Janssen et al., 2013). When monitored outside the context of symptom change, consequences, identity, and emotional responses generally improved or remained stable, with no studies providing evidence of worsening scores over time. One's understanding of their illness (coherence) also improved with time (Bijsterbosch et al., 2009; Janssen et al., 2013; Lawson et al., 2008; Tasmoc et al., 2013), with two studies documenting stability (Dempster et al., 2011; Foster et al., 2008). Control dimensions improved with symptom improvement/time or remained stable in all but three studies reviewed (Astin & Jones, 2006; Bijsterbosch et al., 2009; Dempster et al., 2011), suggesting that longitudinal patterns of control perceptions may be disease specific. Timeline scores generally remained stable with symptom improvements/time (Dempster et al., 2011; Foster et al., 2008; Janssen et al., 2013; Lawson et al., 2008; Rutter & Rutter, 2007), or became more chronic (Astin & Jones, 2006; Bijsterbosch et al., 2009; Tasmoc et al., 2013). No studies examined longitudinal patterns of illness concern.

Considering the cross-sectional and longitudinal illness perception literature, we would expect CLL patients to experience improvements in consequences, identity, personal control, treatment control, emotional responses, and coherence with symptom improvement and time. Although no known studies have examined longitudinal patterns of illness concern, the expectation would be that this dimension would covary with

emotional responses, and thus also improve over time. While timeline varied across studies, most observed stability in this dimension. In combination with the null effects of chronic kidney disease treatment group on timeline reviewed previously, these findings would collectively suggest that timeline would remain stable in the context of CLL treatment.

Focus of the Present Investigation: Illness Perceptions and Chronic Lymphocytic Leukemia

Disease Characteristics and Course

Chronic lymphocytic leukemia (CLL) is a lymphoid malignancy characterized by proliferation of dysfunctional lymphocytes. Most commonly diagnosed among older adults, approximately 70% of patients are older than 65 at initial diagnosis (van den Broek et al., 2012). CLL disproportionally effects men (70%) and Caucasians (90%). The overall 5-year survival is 79.2% (Howlader et al., 2013). CLL is ideal for the study of changing illness stimuli and disease experiences, as there can be three distinct phases of the illness: active surveillance, initiation of a first treatment, and relapsed/refractory disease.

Treatment Trajectory

Active Surveillance. Patients diagnosed with Stage 0 (of 4) disease of the Rai (1975) staging system are asymptomatic or only mildly symptomatic (Hallek et al., 2008). If present, symptoms at this stage may include fatigue, enlarged lymph nodes, night sweats, excessive bleeding/bruising, weakness, unintentional weight loss, and shortness of breath. A recent report indicated that 80% of active surveillance patients

reported at least one physical symptom, and that symptoms were positively associated with anxiety/depressive symptoms and cancer-specific stress (Morrison, Flynn, Jones, Byrd, & Andersen, 2016). These early stage patients are typically monitored without treatment until disease progression, a process known as active surveillance. The duration of surveillance is heterogeneous, ranging from months to years, with approximately 30% of patients never requiring treatment (Dighiero, 2003). Overall, CLL patients on active surveillance have reported poorer quality of life compared to the general population (Else et al., 2008)

Treatment Initiation. Treatment is indicated for patients with progressive disease (Hallek et al., 2008). Of the following, one must be present: 1.) anemia (low hemoglobin) and/or thrombocytopenia (low platelet count), 2.) enlargement of the spleen (splenomegaly) and/or liver (hepatomegaly), 3.) "massive" lymph nodes (at least 10cm [4 inches] in longest diameter), or 4.) rapid progression of lymphocytosis (white blood cell counts; Hallek et al., 2008). At least one constitutional symptom also must be present, including unintentional weight loss, impairing fatigue, and fever or night sweats without evidence of infection. Thus the "illness stimulus" at this treatment initiation stage differs from active surveillance predominantly in terms of symptom severity, though some signs and symptoms are exclusive to patients recommended for treatment (i.e., organ enlargement, anemia, thrombocytopenia).

Studies comparing active surveillance and treated patients on anxiety and depressive symptoms have not found group differences (Holzner et al., 2004; Levin, Li, Riskind, & Rai, 2007; van den Broek et al., 2015). Physical functioning and symptom burden, however, have been documented as poorer among patients initiating a first

treatment relative to those under surveillance (Levin et al., 2007; van den Broek et al., 2015). Patients responsive to therapy reach quality of life scores equivalent to the general population, whereas patients with disease progression report clinically significant reductions (Else et al., 2012). Despite advancements in front-line therapies and the lengthening of first remission (Veliz & Pinilla-Ibarz, 2012), patients inevitably relapse.

Relapsed/Refractory Disease. Upon exhibiting disease progression after successful front-line treatment (relapse), or failing to respond to treatment (refractory), patients are considered relapsed/refractory. The relapsed/refractory population is heterogeneous, ranging from patients with a first remission of several years to those with a history of multiple treatment failures in rapid succession. Furthermore, the prognosis and clinical management of relapsed/refractory patients differs significantly from those initiating a first treatment, as subsequent treatment options generally become more toxic and induce shorter remissions (Chanan-Khan et al., 2006; Shindiapina & Awan, 2016). Certain genetic abnormalities, such as a deletion on chromosome 17p (del17p), can confer risk for even shorter remissions under conventional therapies. Relative to those initiating a first treatment, relapsed/refractory patients experience increased physical symptom burden (Pashos et al., 2013).

Westbrook, Maddocks, & Andersen (2016) examined illness perceptions as predictors of cancer-specific stress and depressive symptoms in CLL patients with relapsed/refractory disease. The authors found that illness perceptions accounted for 25% and 36% of the variance in cancer-specific stress and depressive symptoms, respectively. Specifically, consequences and emotional responses were significantly associated with both outcomes. Illness concern was also concurrently related to cancer-specific stress.

Importantly, relationships were observed while controlling for disease relevant variables such as number of prior treatments, age, and presence of physical comorbidities, underscoring the relevance of illness perceptions to psychological outcomes in relapsed/refractory CLL.

Stimulus Changes in Relapsed/Refractory CLL with Treatment. Study of illness perceptions in relapsed/refractory patients is particularly timely, as only recently have targeted therapies such as ibrutinib been developed which can induce durable remissions. Ibrutinib disrupts mechanisms that support CLL-cell proliferation, with a recent clinical trial reporting overall survival rates of 83% at a median of 26 months (Byrd et al., 2013). Treatment with ibrutinib has been associated with minimal toxicities (Burger et al., 2014; Byrd et al., 2015), allowing for examination of illness stimulus change in a cancer sample that is not confounded by toxicities common to conventional chemotherapies (e.g., nausea, fatigue, neuropathy). In a recent trial (Byrd et al., 2015), the most common adverse events were bleeding (easy bruising and petechiae) and diarrhea, occurring in 61% and 58% of patients, respectively.

Data show responses to ibrutinib and corresponding changes in biological parameters occur rapidly. Byrd and colleagues (2013; 2015) reported that 78% of relapsed/refractory CLL patients displayed therapeutic lymphocytosis (elevated serum levels of white blood cells) by the 7th day of drug administration, with the median time to an initial drug response being 2 months. In collaboration with Byrd and colleagues, we have studied this clinical phenomenon (Figure 2; Weiss et al., under review). The initial spike in lymphocyte count is hypothesized to occur due to release of leukemic white blood cells from the lymph nodes and spleen into the blood stream (Woyach et al., 2014),

and stabilizes after 5-6 months of treatment. This is further corroborated by data from Farooqui and colleagues (2015), who demonstrated that lymph node and spleen volumes decreased by 50% in the majority of patients (70% for lymph nodes; 79% for spleen) within 2 months of treatment. Hemoglobin values have also exhibited rapid improvements over the first 5-6 months of ibrutinib treatment, followed by slower, continued improvements thereafter (Byrd et al., 2015).

Collectively, these clinical ibrutinib data provide rationale for the timing of illness perception assessments for Study 2. As the initial spike in lymphocyte count occurs by 2-months of treatment and stabilizes by 5-months of treatment, Study 2 will examine illness perception change with stimulus changes documented at Month 2 (Cycle 3, Day 1) and Month 5 (Cycle 6, Day 1). These time points also overlap with the median time to drug response (2-months) and rapid changes in lymph node size, organ enlargement, and hemoglobin.

Aims and Hypotheses

Study 1: Illness Perception Comparison by Group

Leveraging Leventhal's Self-Regulatory Model, a cross-sectional, three group design (Figure 3) will be used to contrast illness perceptions between CLL patients differing by phase of CLL treatment: Active Surveillance (AS), Initiating a First Treatment (FT), and initiating treatment for Relapsed/Refractory (RR) disease.

Aim 1. To determine the illness perceptions of patients in the three CLL groups.

- Hypothesis 1A. As previous studies have shown greater symptom severity to covary with more negative illness perceptions (e.g., Edelstein et al., 2012; Dalbeth et al.,

2011; Greco et al., 2015; Pretorius et al., 2014), we hypothesize that identity, consequences, personal control, treatment control, emotional responses, and concern will be most favorable among patients with the least severe symptoms, such that AS patients endorse the most favorable scores on these dimensions, followed by FT, then RR. As most prior studies have not observed relationships between symptom severity and timeline (e.g., Chisari & Chilcot, 2017; Dalbeth et al., 2011; De Gucht, 2015; Edelstein et al., 2012), we do not anticipate that we will detect group differences in this dimensions.

- Hypothesis 1B. As previous studies have shown one's perception of how well they understand their condition to improve with time (Bijsterbosch et al., 2009; Janssen et al., 2013; Lawson et al., 2008; Tasmoc et al., 2013), we hypothesize that coherence scores will be most favorable among patients with the greatest level of experience with CLL via treatment receipt, such that RR patients endorse the highest scores on this dimension, followed by FT, then AS.

Study 2: Illness Stimulus Change

Using a longitudinal design with three assessment time-points, Study 2 will determine the relationship between changes in CLL illness stimuli and changes in illness perceptions among patients with relapsed/refractory disease. On the basis of our prior data (see Figure 2; Weiss et al., under review) and others (Byrd et al., 2013, 2015; Farooqui et al., 2015; Woyach et al., 2014) a change in CLL illness stimuli will occur from baseline to Month 2 and Month 5.

Aim 1 (Figure 4). Determine the relationship between CLL illness stimuli (i.e., fatigue, lymph node volume, organ enlargement [yes vs. no], cell counts [lymphocyte (white blood cell count), hemoglobin]), and illness perceptions among patients with relapsed/refractory disease at pre-treatment baseline.

- Hypothesis 1A. Previous studies have shown greater symptom severity to covary with less favorable scores on total illness threat, consequences, identity, personal control, treatment control, emotional responses, and concern (e.g., Costa et al., 2015; Edelstein et al., 2012; Dalbeth et al., 2011; Greco et al., 2015; Pretorius et al., 2014). Thus, we hypothesize that more severe CLL stimuli (fatigue, lymph node volume, lymphocyte count, and hemoglobin) will covary with less favorable scores on these dimensions. We do not expect to detect associations between CLL stimuli and timeline of coherence.
- Hypothesis 1B. Following the same rationale as Hypothesis 1A, we hypothesize that patients with organ enlargement will endorse less favorable scores on total illness threat, consequences, identity, personal control, treatment control, emotional responses, and concern than those without organ enlargement. We do not expect to detect group differences in coherence or timeline.

Aim 2. To determine illness perception change in the time from Baseline to Month 2 and Baseline to Month 5.

- Hypothesis 2A. Previous longitudinal studies have demonstrated that consequences, identity, personal control, treatment control, emotional responses, and coherence improve with illness stimulus improvements and time (Astin & Jones, 2006; Bijsterbosch et al., 2009; Foster et al., 2008; Janssen et al., 2013; Lawson et al., 2008;

Tasmoc et al., 2013). Thus, we hypothesize that these dimensions, as well as total illness threat and concern, will be improved at Month 2 and Month 5 relative to baseline. We do not anticipate changes in timeline.

Aim 3 (Figure 5). To determine whether changes in illness stimuli from Baseline to Month 2 and Baseline to Month 5 are predictors of 2-month and 5-month changes in illness perception.

- Hypothesis 3A. We hypothesize that changes in CLL illness stimuli from Baseline to Month 2 and Baseline to Month 5 will predict 2- and 5-month change in total illness threat, consequences identity, personal control, treatment control, emotional responses, and concern. We do not anticipate that stimulus changes will predict changes in timeline and coherence.

Chapter 2: Method

Study 1

Participants

A total of 330 patients with CLL participated from three intact groups: active surveillance (AS; n=100), initiating a first treatment (FT; n=78), and initiating treatment for relapsed/refractory disease (RR; n=152). Overall, the majority was male (63%) and Caucasian (98%) with a mean age of 62.2 years. Most were partnered (86%), had some college education or beyond (70%), and 43.8% reported an annual household income exceeding $100,000.

Design and Procedure

A three group, cross-sectional design was used. The Institutional Review Board of a university-affiliated, National Cancer Institute-designated comprehensive cancer center granted ethical approval for all procedures. Active surveillance patients were recruited during routine surveillance appointments and completed a packet of self-report questionnaires over the telephone with research staff. Patients initiating treatment for previously untreated or relapsed/refractory CLL completed a packet of self-report questionnaires as they were screened and enrolled into investigational trials (NCT01589302, NCT02296918, NCT02427451, NCT02518555) of targeted CLL

therapies. Patients unable to complete the assessment during screening did so within two-weeks before treatment began.

Eligible patients were adults aged 18 years or older with a physician confirmed diagnosis of CLL and an Eastern Cooperative Oncology Group performance status of 0-2. Medical inclusion criteria (e.g., normal organ function) were required for patients beginning a treatment. Patients with systemic, life threatening medical comorbidities, recent major surgery or medical procedures, active or secondary cancers, or severe psychiatric illness were excluded.

One-hundred twenty-six active surveillance patients provided informed consent. Three individuals were found to be ineligible, 11 did not participate due to loss of interest, and 12 did not provide illness perception data, resulting in 100 active surveillance participants (80% accrual rate). Among patients initiating treatment for previously untreated or relapsed/refractory disease, 36 provided consent but were later found to be ineligible, resulting in 230 patients initiating treatment (86% accrual rate).

Measure

The Brief Illness Perception Questionnaire (BIPQ; Broadbent et al., 2006) is a 9-item self-report measure used to assess mental representations of illness. The BIPQ uses a single-item scale approach to assess perceptions on a continuous linear 0 to 10-point scale (see Appendix C for scale anchors). Five items assess cognitive illness representations: consequences, timeline, personal control, treatment control, and identity. Two items assess emotional representation of illness: concern and emotional responses. One item assesses illness coherence, a metacognitive dimension reflecting how well an

individual feels they understand their illness. A total score reflecting one's overall perception of an illness (e.g., "total illness threat") can be calculated through reverse-scoring the positively-valenced items (i.e., personal control, treatment control, and coherence) and summing across all items. Scores range from 0 to 80, with higher scores indicating a more negative illness perception. During data collection for active surveillance patients, the treatment control dimension ("How much do you believe treatment can help your illness?") was excluded. Six-week test–retest reliability for the items ranges from .42 to .75 (Broadbent et al., 2006). Concurrent validity with relevant psychological and biological measures, discriminant validity across illnesses, and predictive validity in different disease groups has been reported (Broadbent et al., 2015, 2006).

Analytic Strategy

Sociodemographic differences between groups were tested using one-way ANOVA for continuous variables (i.e., age), and chi-square tests for nominal variables (i.e., gender, marital status, education level, and household income). Descriptive statistics then summarized means, standard deviations, and ranges of all illness perception dimensions. Primary group differences in illness perceptions were tested using one-way analysis of variance (ANOVA). First, normality and homogeneity of group variances were assessed. Skewed data were log-transformed, and Welch's ANOVAs were conducted to confirm group differences for heteroscedastic variables. For the six illness perception dimensions for which a hypothesized trend of group differences was anticipated (i.e., consequences, identity, concern, emotional representation, coherence,

and personal control), pre-planned comparisons were used. Planned comparisons are robust to group differences in sample size, do not require homogenous group variances, and are preferred when trends in group means are anticipated (Quinn & Keough, 2002; Hilton & Armstrong, 2006; Rosenthal & Rosnow, 2008). Two comparisons tested a linear trend of increasing group means: AS to FT (coded -1, 1, 0) and FT to RR (coded 0, -1, 1). Although pre-planned comparisons were used, a supplementary table displaying group comparisons using Tukey post-hoc tests is provided for interested readers (Supplementary Table 3). Substantive results did not differ on the basis of comparison approach. As the treatment control item was administered to FT and RR groups only, this comparison was made using an independent samples t-test. As there was no a priori expectation of group differences for the timeline dimension, ANOVA with post-hoc tests (Tukey) was employed and a Bonferroni corrected p-value of .017 (.05/3) applied. All analyses were performed using IBM SPSS 20.0 for Windows.

We considered sociodemographic variables (age, gender, marital status, education level, and household income) as control variables for group comparison analyses. Race was not considered due to lack of variability in the sample. All candidate control variables were correlated with each illness perception dimension collapsing across groups. Candidate control variables significantly associated with an illness perception dimension were included as covariates in their respective analyses.

Chapter 3: Results

Study 1

Preliminary

Sociodemographic and descriptive characteristics by patient group are displayed in Table 1. Age significantly differed between CLL treatment groups, $F(2, 323) = 6.615$, $p = .002$. Post-hoc comparisons indicated relapsed/refractory patients were significantly older (M=64.08, SD=10.79) than those initiating a first treatment (M=59.03, SD=10.38). There was also an association between CLL treatment group and gender, $\chi^2(2) = 7.69$, $p = .021$, Cramer's V = .15. Examination of adjusted standardized residuals (Sharpe, 2015) indicated that in the relapsed/refractory group there were fewer females (30%) and more males (70%) than would be expected on the basis of no association between gender and CLL treatment group.

Distributions for all illness perception dimensions were non-normal; thus analyses were conducted on log-transformed variables. Results did not differ on the basis of transformation, so untransformed results are presented for ease of interpretation. All dimensions met assumptions for homogeneity of variance between groups except for identity, coherence, and timeline. For these exceptions, group differences were confirmed with Welch's ANOVAs. As unequal sample sizes such as those in the present study can influence the homogeneity of variance assumption (Parra-Frutos, 2013), and as

substantive results did not differ by ANOVA approach, conventional ANOVA results are displayed below.

Regarding covariate selection, age was significantly associated with emotional responses (r = -.172, p = .002), and was thus included as a covariate in that analysis. There were no significant associations between illness perceptions and gender, marital status, education level, or income.

Primary

Identity

Groups differed in the extent to which they perceived CLL symptoms (See Figure 6), $F(2, 327) = 28.87$, $p < .001$, $\eta^2_p = .150$. Consistent with hypotheses, planned contrasts revealed a significant linear trend of increasing group means, $F(1, 327) = 56.55$, $p < .001$, such that AS patients perceived the fewest symptoms (M = 1.96, SD = 2.05), followed by FT (M = 3.10, SD = 2.74), then RR (M = 4.46, SD = 2.81). Importantly, these significant effects provide a "validity check" and confirm the assumption that groups differ in CLL symptoms.

Consequences

Groups differed in the extent to which they perceived CLL as impacting their lives, $F(2, 326) = 16.93$, $p < .001$, $\eta^2_p = .094$. Consistent with hypotheses, AS patients perceived the fewest consequences (M = 2.74, SD = 2.56), followed by FT (M = 4.03, SD = 2.92), then RR (M = 4.84, SD = 2.89).

Concern

Groups differed in the extent to which they reported concern about CLL, F(2,

326) = 14.31, $p < .001$, $\eta^2_p = .081$. Consistent with hypotheses, planned contrasts revealed a significant linear trend of increasing group means, $F(1, 326) = 28.60$, $p < .001$, such that AS patients reported the least concern ($M = 5.38$, $SD = 3.16$), followed by FT ($M = 6.58$, $SD = 3.12$), then RR ($M = 7.44$, $SD = 2.78$).

Coherence

Groups differed in the extent to which they believed they understood CLL, $F(2, 327) = 8.46$, $p < .001$, $\eta^2_p = .049$. Although there was a significant linear trend of group means in the hypothesized direction, $F(1, 327) = 15.34$, $p < .001$, planned contrasts indicated only AS ($M = 7.31$, $SD = 2.26$) and FT ($M = 8.23$, $SD = 1.77$) differed ($p = .002$), with those initiating a first treatment endorsing greater understanding of CLL than those under surveillance. The difference in coherence scores for FT ($M = 8.23$, $SD = 1.77$) and RR ($M = 8.30$, $SD = 1.86$) groups was not significant ($p = .793$).

Personal Control

Groups differed in the extent to which they believed they personally could control CLL, $F(2, 323) = 7.49$, $p = .001$, $\eta^2_p = .045$. Contrary to hypotheses, the linear trend of group means was not significant ($p = .404$). Planned contrasts indicated personal control beliefs were highest for FT patients ($M = 5.01$, $SD = 3.36$) relative to both RR ($M = 3.65$, $SD = 2.77$) and AS ($M = 3.32$, $SD = 3.10$). The latter two groups did not differ ($SE = .390$, $p = .785$).

Timeline

Groups differed in how long they believed CLL would last, $F(2, 321) = 20.24$, $p < .001$, $\eta^2_p = .112$. Contrary to hypotheses, AS patients believed that CLL would last the longest ($M = 9.24$, $SD = 1.82$), followed by RR ($M = 7.39$, $SD = 2.78$), then FT ($M =$

6.95, *SD* = 3.26). Post-hoc comparisons indicated timeline scores for AS patients were higher relative to both RR (*SE* = .293, $p < .001$) and FT (*SE* = .414, $p < .001$) groups. The latter two groups did not differ (*SE* = .436, $p = .566$).

Treatment Control

Groups differed in the extent to which they believed CLL treatment would be helpful, $t(228) = 2.90$, $p = .004$, $d = .403$. Consistent with hypotheses, FT patients believed more strongly that treatment would be helpful (*M* = 8.94, *SD* = 1.96) than RR patients (*M* = 8.14, *SD* = 1.87).

Emotional Responses

Groups did not differ in the extent to which they felt CLL impacted them emotionally ($p = .225$).

Chapter 4: Discussion

Study 1

Foundational theoretical work in illness perceptions (Leventhal et al., 1980) highlighted symptoms and prior experiences with health threats as central to the formation of a corresponding mental representation. In an empirical test of this postulate, the current study contrasted illness perceptions between three groups of patients with CLL: active surveillance, initiating a first treatment, and initiating treatment for relapsed/refractory disease. Differing naturally on symptoms and disease experiences theorized as key determinants of illness perceptions, these groups provided an ideal context for better understanding factors relevant to patients' mental representations of illness. While consequences, identity (symptoms), and concern were significantly poorer among patients at each successive phase of treatment, perceptions of personal control and helpfulness of treatment (treatment control) were most favorable among patients initiating treatment for the first time. Perceptions of how well one understands CLL (coherence) and and how long CLL will last (timeline) were poorest among active surveillance patients. Despite these differences, all groups reported equivalent emotional responses to CLL.

Notably, consequences, identity (symptoms), and concern were significantly poorer among patients at each successive phase of treatment. Mapping onto a clinical

picture of increasing stimulus severity as CLL patients transition from surveillance to a first treatment and beyond (Levin et al., 2007; Pashos et al., 2013; van den Broek et al., 2015), these findings support Leventhal's postulate that greater somatic stimulus severity is associated with more negative illness perceptions. While the illness concern finding is consistent with self-regulatory theory, it is noteworthy that emotional responses, an additional dimension of emotional representations (Figure 1) did not differ between groups. The concern item was included in the Brief Illness Perception Questionnaire to capture worry (Broadbent et al., 2015), which is not an emotional response per se, but a chain of thoughts and images, which are laden with negative affect (Borkovec, Robinson, Pruzinsky, & DePree, 1983). It could be that worry increases throughout the course of CLL treatment, but not overall rates of negative emotions such as sadness or anger. van den Broek and colleagues (2015) provide support for this hypothesis, observing differences between CLL treatment groups (surveillance vs. on treatment) on several domains of cancer-specific worry (e.g., personal health, future, cancer recurrence) but no group differences in anxiety or depression. Future work in this population may benefit from use of cancer-specific worry scales when evaluating and monitoring psychological functioning.

Also consistent with self-regulatory theory, group differences in the perceived helpfulness of treatment (treatment control) mapped onto increasing stimulus severity across the CLL trajectory, with those initiating a first treatment believing more strongly that treatment would be helpful than those initiating treatment for relapsed/refractory disease. While also in line with previous research linking symptom severity and treatment control (Dalbeth et al., 2011; Edelstein et al., 2012; Pretorius et al., 2014), the

treatment history of relapsed/refractory patients is important to consider. Average number of previous CLL therapies for patients was 3.5 (*SD* = 2.6), with some relapsing and/or failing to respond to upwards of 16 prior therapies. Thus, patients conceivably learned that treatment effects do not remain (i.e., relapse), and may be aware that subsequent treatments are less effective in controlling CLL. Nevertheless, perceptions of the helpfulness of treatment were high for both groups (FT = 8.9/10; RR = 8.1/10), reflecting that, despite ultimately being incurable, patients in this context had high levels of confidence in the ability of treatment to be helpful for at least some period of time.

Contrary to treatment control findings, personal control did not vary across groups in a manner that would be expected on the basis of stimulus severity alone. It was anticipated that personal control would be highest among those with less severe illness stimuli (i.e., active surveillance). Instead, personal control was highest among those initiating a first treatment, followed by relapsed/refractory and active surveillance groups that did not differ. Relevant to self-regulatory theory, this finding implies that personal control may be less influenced by symptom experiences than originally hypothesized. It could be that the progression of symptoms characteristic of those requiring a first treatment provide more opportunities (or a first opportunity) for CLL patients to mobilize coping behaviors and request information from medical providers about how to best control their symptoms. Surveillance patients are frequently told that their disease requires no immediate action (Evans, Ziebland, & Pettitt, 2012). Relapsed/refractory patients, at the other end of the spectrum, may feel less personal control over CLL as a result of their cycling of treatment and relapse. Future longitudinal research documenting

changes in treatment control as patients transition from surveillance to a first treatment and beyond may help clarify the nature of these relationships.

Coherence also differed between groups, with patients initiating a first or subsequent treatment endorsing greater understanding of CLL than those under surveillance. These findings are largely consistent with expectations of self-regulatory theory that those with greater prior experience with a condition would *learn* from their experiences and thus endorse greater understanding of the condition relative to those with less exposure to the disease. Findings are also consistent with previous research (Bijsterbosch et al., 2009; Janssen et al., 2013; Lawson et al., 2008; Tasmoc et al., 2013), and may reflect a general tendency across illnesses to learn more about one's condition through continued interactions with physicians and treatment experiences. It is important to note, however, that there is evidence that CLL surveillance patients experience unique dissatisfaction regarding information provided by medical professionals. In Evans and colleague's (2012) qualitative report, surveillance patients (N=12) commonly expressed a desire for more information, highlighting their uncertainty regarding which symptoms to monitor or how the disease or its treatment may affect them in the future. In combination with results from the current study, these findings suggest that surveillance may represent a period of heightened uncertainty for CLL patients as they face an indolent disease with an undetermined course. Future studies might assess the unique knowledge needs of this group and examine whether physician-patient communication can be improved.

As perceptions of how long one's illness will last (timeline) have generally been unrelated to symptom severity and time, we hypothesized that this dimension would not differ by CLL group. Contrary to this hypothesis, differences were observed, with active

surveillance patients believing their illness would last the longest, followed by both treatment groups that did not differ. On the basis of self-regulatory theory, it would be expected that those with the greatest stimulus severity would perceive their illness as lasting for the longest duration of time. However, results of the current study, in addition to the prior literature observing null effects between symptom severity and timeline (De Gucht, 2015; Edelstein et al., 2012) suggest that this may not be the case. The context of treatment for patients in the current study may provide insight into the pattern of observed group differences. Patients initiating a first or subsequent treatment were enrolled in clinical trials of novel targeted therapies at a National Cancer Institute-designated Comprehensive Cancer. These factors may have bolstered treatment control beliefs and influenced the lower timeline scores observed among treatment groups relative to their surveillance counterparts. Examination of CLL patients in community settings or outside the context of clinical trials may yield different patterns of control and timeline beliefs.

A primary strength of the current study is its theory-based analysis of the CLL patient experience, which is particularly appropriate given the unique disease trajectory of CLL relative to other cancers. Further, patients initiating treatment completed the illness perception assessment before treatment began, preventing the potential confounding effects of anti-cancer therapy (e.g., nausea, fatigue, neuropathy). Additionally, the group comparison design did not require self-report of symptom severity. Self-regulatory theory indicates that type and severity of symptoms are critical determinants of illness perceptions, yet when considering this question, studies reliant on patients' self-report encounter methodological issues of common measurement and

conceptual overlap. For example, individuals who perceive more severe symptoms (identity), are likely to report more severe symptoms, complicating inferences about the relationship between severity and illness perceptions. One way to circumvent this is to contrast illness perceptions among groups known or presumed to differ on symptom severity as done here (and corroborated by group differences on the identity item). Future studies could also include objective disease markers (e.g., lymph node volume or hemoglobin counts in CLL) as previously done in a select group of studies from other disease groups (Dalbeth et al., 2011; Edelstein et al., 2012; Greco et al., 2015).

Limitations are also considered. Patients initiating treatment were doing so in the context of clinical trials, which often underrepresent minorities and older adults (Eichhorst et al., 2009; Heller et al., 2014). Thus, our sample was younger (mean age=62.2 years) and more likely to be Caucasian (98%) than rates recorded in national CLL samples (median age at diagnosis=71; 90% Caucasian; Miller et al., 2016; Shenoy et al., 2011). As a low incidence disease, CLL patients are often treated at regional centers, which may produce expectancy effects that differ from those of a community treatment setting. Lastly, although the cross-sectional design provides an ideal first step in the context of a disease where several years may pass between treatment phases, a longitudinal design, perhaps targeting critical change periods (e.g., patients transitioning from surveillance to a first treatment), would help clarify mechanisms giving rise to group differences.

In conclusion, novel data contrasting illness perceptions from three phases of CLL treatment affirmed theoretical postulates (Leventhal et al., 1980) that symptoms and disease experiences are important determinants of mental representations of illness.

While some dimensions appeared to map closely onto symptom experiences (i.e., consequences, identity, concern) others may have been more influenced by factors such as knowledge acquired through interactions with the medical system (i.e., coherence, personal control) or the context of treatment itself (i.e., timeline, treatment control). Future work is needed, particularly in the form of longitudinal studies and those that use objective disease severity markers, to continue to garner a better understanding of factors that influence patient perceptions of illness.

Chapter 5: Method

Study 2

Participants

Sociodemographic, disease, and treatment characteristics for Study 2 participants (N=152) are displayed in Table 2. Overall, the majority of participants were male (70%), and Caucasian (97%), with a mean age of 64.1 years (*SD* = 10.79; range= 26-91). Most were partnered (85%), had some college education or beyond (68%), and had an annual household income exceeding $50,000 (55%). Patients had received on average 3.47 (*SD* = 2.61; range 1-16) prior CLL therapies and 78 (51%) participants had disease with del17p. The average Charlson Comorbidity Index score was 2.53 (*SD* = 0.99; range = 2-9); all participants received 2 points for their CLL diagnosis.

Design and Procedure

A single group, observational, longitudinal design was used. The Institutional Review Board of a university-affiliated, National Cancer Institute-designated comprehensive cancer center granted ethical approval for all procedures. See Study 1 for accrual description. Individuals with relapsed/refractory CLL initiating treatment with ibrutinib were assessed pre-drug on the first day of treatment (Cycle 1, Day 1), and at 2-months (Cycle 3, Day 1) and 5-months (Cycle 6, Day 1) later. Assessment time-points are referred to as baseline, Month 2, and Month 5. Physical examinations, blood draws,

computed tomography (CT) scans, and psychological assessments were completed at each time point.

Measures

Outcome

Illness Perception. See Study 1 for description of illness perception assessment.

Predictors (Illness Stimuli)

Fatigue. The Fatigue Symptom Inventory (FSI; Hann et al., 1998) is an 11-item questionnaire used to measure the frequency, severity, and daily pattern of fatigue, as well as its impact on quality of life in the past week. A 7-item subset of the FSI, the Total Disruption Index, was used and measures the extent to which fatigue interferes with multiple aspects of life (e.g., enjoyment of life, ability to concentrate, relations with other people) in the past week. Participants rated items on an 11-point Likert scale ranging from 0=no interference to 10=extreme interference. Total scores range from 0 to 70, with higher scores indicating greater fatigue interference. Internal consistency ranged from 0.93 to 0.95 across time points.

Lymph Node Volume. All patients received computed tomography (CT) scans to assess and monitor lymph node size. Nodes were measured bi-dimensionally in centimeters by trial staff. The "sum of the products of the greatest perpendicular diameters" (SPD) was used as a measure of lymph node volume. This measure creates a product term for the largest 2 diameters of each measurable lymph node and sums them. It is used in leukemia clinical trials and correlates with therapeutic drug response (Byrd et al., 2015).

Organ Enlargement Determination. Physicians assessed patients' liver and spleen clinically by palpation, making the decision of enlarged ("abnormal") or not ("normal"). Data were scored 1 = abnormal vs. 0 = normal.

Lymphocyte Count and Hemoglobin. Lymphocyte count (mcL) and hemoglobin (g/dL) values were extracted from medical record forms summarizing cell counts.

Covariates

Sociodemographic and General Health. Sociodemographic data were obtained via self-report and include age, gender, race, education, income, partner status, and employment status. Data regarding number of previous CLL therapies and medical history were extracted from medical records. Also calculated was the Charlson Comorbidity Index (CCI; Charlson, Pompei, Ales, & MacKenzie, 1987), an estimate of the prevalence of physical health comorbidities. The index is comprised of 19 conditions, each weighed from 1-6 based on the severity of the condition and its relation to mortality. The total score, which ranges from 0-37, was used. The CCI has been validated for patients with chronic illness, including cancer (Charlson et al., 1987).

Depressive Symptoms. The Beck Depression Inventory-2nd edition (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report instrument used to assess severity of depressive symptoms. Patients described the way they have been feeling during the past month by rating each item (sadness, pessimism, loss of pleasure) on a scale from 0 to 3. Items were summed, with higher scores indicating more depressive symptoms. Two different scores may be calculated, summarizing both the cognitive-affective (Items 1-14) and the somatic (Items 15-21; Beck, Steer, & Garbin, 1988) symptoms of depression. As the somatic symptoms may be confounded by physical symptoms commonly experienced

by cancer patients, analyses were conducted using the cognitive-affective subscale. The scores on the cognitive-affective subscale can range from 0 to 42. Internal consistency ranged from 0.80 to 0.90 across time-points.

Analytic Strategy

Descriptive statistics summarized means, standard deviations, and ranges of all CLL illness stimuli and illness perception variables. If a participant did not complete at least 75% of scale, their score was not included in analyses. For those missing less than 25% of a scale, their score was calculated by averaging across the number of completed items.

Primary Analyses

Pre-treatment data. Spearman correlations examined the pre-treatment associations between illness perceptions and fatigue, lymph node volume, lymphocyte count, and hemoglobin. Independent samples t-tests examined group differences in illness perception between patients with (coded 1) and without (coded 0) organ enlargement.

Longitudinal data. Repeated measures analysis of variance (ANOVA) examined changes in all illness stimuli and illness perceptions during the first 5-months of treatment. For primary analyses (i.e., fatigue, lymph node volume, and organ enlargement), hierarchical multiple linear regression tested if changes in CLL illness stimuli predicted changes in illness perception. First, change scores (Month 2 – Baseline; Month 5 – Baseline) for each dimensional stimulus variable were calculated. For

changes in organ enlargement status, an indicator variable was created to identify whether an individual's organ enlargement status changed (coded 1) or remained the same (coded 0) at Month 2 and Month 5 relative to Baseline. Control variables considered for analyses were sociodemographic (gender) and biomedical (number of prior therapies, Charlson Comorbidity Index, del17p) variables significantly correlated ($p<.05$) with the dependent variable. Regression models predicting illness perceptions at Month 2 and Month 5 were constructed via entry in steps as follows: 1.) illness perception dimension at baseline; 2.) control variables significantly correlated with outcome; 3.) illness stimulus change score/organ enlargement indicator variable.

Secondary Analyses

To test the influence of changes in cell counts (lymphocyte count and hemoglobin) from Baseline to Month 2 and Baseline to Month 5 on illness perception change, the primary regression analytic strategy for longitudinal data was repeated with cell count changes as a predictor in the final step of the model.

Exploratory Analyses

Control for Depressive Symptoms. Previous data from our group (Westbrook et al., 2016) indicate that more negative CLL illness perceptions covary with greater levels of depressive symptoms. In order to examine whether the relationship between illness stimuli and illness perceptions exists independent of the influence of depressive symptoms, follow-up regressions controlling for depressive symptoms were conducted. Specifically, each of the longitudinal regression models predicting total illness threat at

Month 2 (5 models, 1 for each illness stimulus variable) and Month 5 (5 models, 1 for each illness stimulus variable) were amended to included depressive symptoms as a control. Regression models predicting illness perceptions at Month 2 and Month 5 were constructed via entry in steps as follows: 1.) illness perception dimension at baseline; 2.) control variables significantly correlated with outcome; 3.) depressive symptoms, 4.) illness stimulus change score.

Data Availability

Of 152 patients completing a baseline assessment (Figure 7), 146 (96%) were enrolled at Month 2, and 135 (89%) were enrolled at Month 5. By 5-months, 17 (11%) participants died (N=9) or were removed from the study due to adverse drug-related events (N=8; e.g., systemic infection).

Chapter 6: Results

Study 2

Descriptive

Baseline summary statistics for illness perceptions are displayed in Table 2. Consistent with self-regulatory theory, there was variability in illness perceptions. Scores on the total illness threat composite ranged from 8 to 59 (mean=37.67, median=37.00, *SD*=10.12, maximum range 0 to 80), which is comparable to scores observed in a recent report of 182 mixed-site (i.e., breast, urological, gynecological, gastrointestinal) cancer survivors (M=39.93; Foster et al., 2015). Concerning individual dimensions (maximum range=0-10), patients endorsed understanding of CLL (coherence; *M*=8.30, *SD*=2.77) and perceived that treatment would be helpful (treatment control; *M*=8.17, *SD*=1.87). However, patients also reported concern about CLL (illness concern; *M*=7.44, *SD*=2.77) and believed their illness would last a long time (timeline; *M*=7.39, *SD*=2.78). Patients endorsed consequences (*M*=4.84, *SD*=2.89) and symptoms (identity; *M*=4.46, *SD*=2.81) related to CLL. Patients endorsed negative emotions (emotional responses; *M*=3.76, *SD*=2.92) related to CLL and overall did not view CLL as a condition they could personally control (*M*=3.65, *SD*=2.77).

Summary statistics for baseline illness stimulus variables are displayed in Table 2. The average Fatigue Symptom Inventory (FSI) score was 16.15 (*SD*=15.59), which is

elevated relative to previous reports of active surveillance CLL patients (*M*=11.4, *SD*=13.1; Morrison et al., 2016), and lower than scores observed among chronic myeloid leukemia patients receiving a tyrosine kinase inhibitor (mean=20.93, *SD*=19.74; Phillips et al., 2013). The median lymph node volume (44.3 cm^2) was within range of that observed in previous CLL samples (e.g., Mato et al., 2015 [median SPD=23.4 cm^2]; Furman, Forero-Torres, Shustov, & Drachman, 2010 [median SPD=87.2cm^2]). Regarding hemoglobin (mean=10.87 g/dL; median=10.60 g/dL; range=6.50-15.40 g/dL), normative levels for healthy adults range from 12-18 g/dL (Billett, 1990), with values below 11 g/dL indicating disease-related anemia in CLL (Hallek et al., 2008). A total of 88 participants (58%) had anemic hemoglobin levels consistent with moderate-to-high risk disease. Baseline lymphocyte counts were elevated (mean=58.37×10^9/L; median=45.58×10^9/L; range=0.30-305.69×10^9/L) relative to normative reference ranges (1.5-3.5×10^9/L), a hallmark of leukemia, and consistent with previous reports in relapsed CLL (Coiffier et al., 2010; Woyach et al., 2014; Byrd et al., 2015). A total of 111 (73%) patients displayed evidence of organ enlargement at baseline, which is comparable to rates (e.g., 80%; Gautier, Bengtson, Liebers, & Cohen, 2006) observed in similar chronic lymphoproliferative leukemias (e.g., hairy cell leukemia).

Aim 1: Baseline concurrent relationships between CLL illness stimuli and illness perceptions

Hypothesis 1A. Greater illness stimulus severity will be associated with less favorable scores on total illness threat, consequences, identity, personal control, treatment control, emotional responses, and concern at baseline. Spearman correlation

coefficients indicated that CLL illness stimuli were related to several illness perception dimensions at baseline (Table 3). Greater fatigue was associated with poorer scores on total illness threat ($\rho = .448$, $p < .001$), consequences ($\rho = .480$, $p < .001$), identity ($\rho = .540$, $p < .001$), and emotional responses ($\rho = .368$, $p < .001$). Lower hemoglobin levels were associated with poorer scores on total illness threat ($\rho = -.183$, $p = .024$), and identity ($\rho = -.225$, $p = .005$). Higher lymphocyte count was associated with more negative emotional responses ($\rho = .208$, $p = .010$). Lymph node volume was not associated with any illness perception dimension. For interested readers, correlations between CLL illness stimuli and illness perceptions at Month 2 and Month 5 are displayed in Table 4.

Hypothesis 1B. Patients with organ enlargement will endorse less favorable scores on total illness threat, consequences, identity, personal control, treatment control, emotional responses, and concern than those without organ enlargement. Independent sample t-tests contrasted illness perceptions between patients with and without organ enlargement at baseline (Table 5). Patients with organ enlargement perceived more negative emotional responses, $t(144) = -2.09$, $p = .039$, than those with no enlargement. Patients with organ enlargement endorsed poorer personal control at $p = .06$, with null effects for remaining dimensions ($ps > .08$).

Aim 2. Longitudinal changes in illness stimuli and illness perceptions

Repeated measures ANOVA results indicated that all illness stimuli improved with time (Table 6). Fatigue improved from baseline to Month 2, and remained stable

from Month 2 to Month 5, $F(1.82, 227.74) = 16.255$, $p < .000$. Lymph node volume decreased, $F(1.06, 137.11) = 110.41$, $p < .000$, and hemoglobin increased, $F(1.56, 206.48) = 59.17$, $p < .000$, from baseline to Month 2, with continued improvement from Month 2 to Month 5. Lymphocyte counts increased from Baseline to Month 2 (therapeutic lymphocytosis), then returned to baseline levels by Month 5, $F(2, 264) = 17.46$, $p < .000$. Changes in organ enlargement status at Month 2 and Month 5 are displayed in Table 7.

Hypothesis 2A. Total illness threat, consequences, identity, personal control, treatment control, emotional representation, concern, and coherence will be improved at Month 2 and Month 5 relative to baseline. As predicted, several illness perceptions improved with time (Table 6): total illness threat, $F(1.66, 209.97) = 32.63$, $p < .000$, consequences, $F(1.75, 215.09) = 16.55$, $p < .000$, identity, $F(1.73, 214.91) = 19.64$, $p < .000$, personal control, $F(2, 250) = 11.425$, $p < .000$, treatment control, $F(13.95, 1.55) = 9.03$, $p < .000$, emotional responses $F(1.79, 225.53) = 23.25$, $p < .000$, and concern, $F(2, 246) = 13.63$, $p < .000$. Change occurred by Month 2 for the majority of these dimensions (i.e., total illness threat, consequences, identity, personal control, concern, emotional responses) and remained stable from Month 2 to Month 5. Departing from this trend, the treatment control dimension did not significantly differ from baseline until Month 5. Treatment control was also the only dimension for which Month 5 levels were significantly improved relative to Month 2. Contrary to Hypothesis 2A, coherence worsened from baseline to Month 2, then returned to baseline levels by Month 5.

Aim 3: Change in CLL illness stimuli predicting residual change in illness perceptions

Preliminary Analyses

Control variables for regression analyses were sociodemographic (i.e., age) and biomedical (number of prior therapies, Charlson Comorbidity Index, and genetic risk [del17p]) variables significantly correlated with an illness perception dimension at Month 2 or Month 5 (Table 8). No candidate control variables were correlated with any illness perception dimension at Month 2. At Month 5, number of prior therapies was associated with total illness threat ($\rho = .224$, $p < .05$), consequences ($\rho = .284$, $p < .01$), and identity ($\rho = .235$, $p < .01$); thus, number of prior therapies was included as a covariate in each regression model predicting total illness threat, consequences, and identity at Month 5.

For consideration of outliers, illness stimuli and illness perceptions were transformed to standardized *z* scores with a mean of 0 and a standard deviation of 1. Per recommendations for moderate-to-large sample sizes (Tabachnick & Fidell, 2013), values greater than 3.3 standard deviations from the mean ($p < .001$ of the *z* distribution, two-tailed) were flagged as outliers of interest. Across the three time points, 3 instances of outliers for fatigue and 5 instances of outliers for lymphocyte count were observed. To reduce the influence of outliers without case deletion, the deviant scores were replaced with the next highest non-deviant raw score per recommendations (Tabachnick & Fidell, 2013). However, results of analyses including fatigue and lymphocyte count did not differ on the basis of outlier correction; thus, results utilizing original values are displayed below. Regarding lymph node volume, Subject 144 had outlier values at baseline (732.17 cm^2, z=8.07), Month 2 (448.42 cm^2, z=8.61), and Month 5 (318.00 cm^2, z=8.55). Subject 87 also had an outlier lymph node volume at Month 2 (217.93cm^2, z=3.87). Correction of these outliers enhanced model fit for lymph node regressions and resulted in an increased number of significant parameters, presented below.

Lastly, residual plots of regression analyses were assessed for normality. Data were square-root transformed if positively skewed, or reflected and then square-root transformed if negatively skewed. As results did not differ substantively on the basis of transformation, untransformed results are presented for ease of interpretation.

Primary Analyses

Hypothesis 3A. Changes in CLL illness stimuli from Baseline to Month 2 and Baseline to Month 5 will predict 2- and 5-month change in total illness threat, consequences, identity, personal control, treatment control, emotional responses, and concern.

Fatigue

Displayed in Table 9 is a summary of all significant effects for Aim 3 analyses. Two-month change in fatigue predicted the residual change from baseline to Month 2 in total illness threat ($\beta = 0.234$; $p = .002$), consequences ($\beta = 0.160$; $p = .037$), and identity ($\beta = 0.314$; $p < .000$) (Table 10). Change in fatigue accounted for an additional 5.2% of variance in total illness threat, 2.4% in consequences, and 9.0% in identity. The positive beta coefficient indicated that as change in fatigue became more negative (i.e., improving fatigue scores), total threat, consequences, and identity decreased. Effects for personal control were as follows: $\beta = -0.141$; $p = .056$. Other dimensions were nonsignificant (*ps* > .252).

Regarding change from baseline to Month 5, effects were replicated for total illness threat ($\beta = 0.299$; $p < .000$), consequences ($\beta = 0.238$; $p = .005$), and identity ($\beta =$

0.380; p <.000). Five-month change in fatigue also predicted residual change in timeline (β = 0.211; p =.010) and emotional responses (β = 0.157; p =.044). Fatigue change accounted for an additional 8.3% of variance in total illness threat, 5.1% in consequences, 11.1% in identity, 4.4% in timeline, and 2.4% in emotional responses. The positive beta coefficients for timeline and emotional responses indicated that as change in fatigue became more negative (i.e., improving fatigue scores), timeline and emotional responses decreased. Effects for other dimensions were nonsignificant (*ps* >.143).

Lymph Node Volume

Two-month change in lymph node volume predicted the residual change from baseline to Month 2 in total illness threat (β = 0.147; p =.043) (Table 11). Change in lymph node volume accounted for an additional 2.2% of variance in total illness threat. The positive beta coefficient indicated that as change in lymph node volume became more negative (i.e., improving lymph node volume), total threat regarding CLL decreased. Effects for other dimensions were nonsignificant (*ps* > .097).

Regarding change from baseline to Month 5, effects were replicated for total illness threat (β = 0.211 p =.007). Five-month change in lymph node volume also predicted residual change in concern (β = 0.216; p =.006). Change in lymph node volume accounted for an additional 5.8% and 3.9% of variance in total illness threat and concern, respectively. Effects for other dimensions were nonsignificant (*ps* >.07).

Organ Enlargement Status

Two-month and five-month change in organ enlargement status did not predict changes in any illness perception dimension (*ps* >.096).

Secondary Analyses

Lymphocyte Count

Two-month change in lymphocyte count did not predict the residual change from baseline to Month 2 in any illness perception dimension (*ps* > .134) (Table 12). Five-month change in lymphocyte count predicted the residual change from baseline to Month 5 in identity (β = 0.168; *p* =.043). Change in lymphocyte count accounted for an additional 2.8% of the variance in identity. The positive beta coefficient indicated that as change in lymphocyte count became more negative (i.e., improving lymphocyte counts), identity decreased. Effects for other dimensions were nonsignificant (*ps* > .073).

Hemoglobin

Two-month change in hemoglobin predicted the residual change from baseline to Month 2 in identity (β = -0.240; *p* =.002) and concern (β = -0.158; *p* =.031) (Table 13). Change in hemoglobin accounted for an additional 5.7% and 2.5% of variance in identity and concern, respectively. The negative beta coefficients indicated that as change in hemoglobin became more positive (i.e., improving hemoglobin values), scores on identity and concern decreased (i.e., improved). Effects for other dimensions were nonsignificant (*ps* > .100).

Regarding change from baseline to Month 5, effects were replicated for identity (β = -0.262; *p* =.002), though not concern. Instead, five-month change in hemoglobin

predicted residual change in total illness threat (β = -0.247; *p* =.002) and consequences (β = -0.267; *p* =.001). Change in hemoglobin accounted for an additional 5.9%, 6.8%, and 6.5% of variance in total threat, consequences, and identity, respectively. The negative beta coefficients indicated that as change in hemoglobin became more positive (i.e., improving hemoglobin), total threat, consequences, and identity decreased. Effects for other dimensions were nonsignificant (*ps* > .108).

Exploratory

Control for Depressive Symptoms

In order to examine whether illness stimulus change predicted illness perception change independent of the influence of depressive symptoms, the 10 total illness threat regression models (five for each illness stimulus at Month 2 and Month 5) were reanalyzed controlling for baseline cognitive-affective depressive symptoms. Of the five models originally predictive of change in total illness threat [1.) change in fatigue at Month 2; 2.) change in fatigue at Month 5; 3.) change in lymph node volume at Month 2; 4.) change in lymph node volume at Month 5; and 5.) change in hemoglobin at Month 5], controlling for depressive symptoms did not alter results.

Chapter 7: Discussion

Study 2

Leventhal's Self-Regulatory Model of Illness Behavior (SRM; 1980) provides a theoretical framework for understanding how individuals respond to health threats and make efforts to reduce or resolve them. The model posits that mental representations of health threats, or illness perceptions, are integral to the selection and implementation of coping behaviors and both directly and indirectly influence psychological and physical health outcomes (Figure 1). Despite extensive research supporting this hypothesis (Broadbent et al., 2015; Dempster et al., 2015; Hagger & Orbell, 2003; McSharry et al., 2011; Richardson et al., 2016), lesser attention has focused on better understanding determinants of illness perceptions (Leventhal et al., 2016; Lowe & Norman, 2017). The current study addressed this gap through empirically testing a fundamental SRM postulate that illness perceptions are influenced by somatic characteristics of the illness stimulus (i.e., symptom severity) and their change over time. Among patients with relapsed/refractory CLL initiating treatment, analyses revealed that changes in fatigue and objective disease markers accounted for significant variance in illness perception change.

Pre-Treatment Findings: Fatigue and Hemoglobin

The SRM posits that somatic stimuli are the "central route" by which illness perceptions are formed (Leventhal et al., 1980; 2011 pp. 153). Meyer, Leventhal, & Gutmann (1985) theorized that humans are fundamentally motivated to protect themselves from health-related danger, and that somatic stimuli provide concrete, salient information that a deviation from normal functioning has occurred. Moreover, while transient, mild deviations from normal functioning are expected, it is the *severity* of the somatic experience that is theorized as particularly relevant to one's perception (Leventhal et al., 1980). Results from the current study provided empirical support for this hypothesis, finding that illness perceptions covaried with both subject and objective stimulus severity at pre-treatment baseline. At the subjective, self-report level, patients with greater fatigue perceived greater overall threat towards CLL, more consequences, a stronger illness identity (symptoms), and more negative emotional responses. This is consistent with previous studies documenting concurrent relationships between self-reported symptom severity and illness perceptions (e.g., Artom et al., 2017; Chisari & Chilcot, 2017; De Gucht, 2015; Knowles et al., 2016) and adds novel data regarding the nature of these relationships in a hematologic malignancy.

At the objective stimulus level, lower hemoglobin levels were associated with an overall poorer perception of CLL (total illness threat), more symptoms (identity), and the perception that CLL would last for a longer duration of time (timeline). Decreases in hemoglobin, particularly to anemic levels, produce salient feelings of fatigue, weakness, lightheadedness, and occasional dizziness or heart palpitations (Hodges, Rainey, Lappin, & Maxwell, 2007). Findings of the current study suggest that illness perceptions are

sensitive to these sensations, consistent with self-regulatory theory and previous research relating objective severity markers to illness perceptions in arthritis and cardiovascular disease (Dalbeth et al., 2011; Edelstein et al., 2012, Greco et al., 2015). Moreover, intercorrelations at Month 2 and Month 5 (Table 4) show that relationships between hemoglobin and illness perceptions became stronger with time. While hemoglobin was associated with total illness threat, identity, and timeline at baseline (correlations ranging from $\rho = -.183$ to $\rho = -.225$), by Month 5 hemoglobin was concurrently associated with a greater number of illness perceptions (total illness threat, consequences, identity, timeline, personal control, and concern) with the strength of associations now ranging from $\rho = -.197$ (personal control, reverse scored) to $\rho = -.390$ (identity). These findings suggest that improvements in hemoglobin and corresponding physical symptoms (e.g., fatigue, lethargy, weakness, heart palpitations) during treatment may be particularly salient to CLL patients, and become more so with time. Given that illness perceptions are the theoretical antecedents of other psychological constructs (e.g., stress, mood), these findings also position hemoglobin as an ideal candidate for use in future biobehavioral CLL studies.

Also relevant are the illness perceptions that were not associated with fatigue and hemoglobin at baseline. Consistent with expectations, no association was detected between these stimulus variables and illness coherence, potentially reflecting that coherence is largely influenced by other factors, such as level of experience with the condition or quality of information received from healthcare professionals. It was also anticipated that, given the predominance of null associations between symptom severity and timeline in prior studies, an association would not be detected between timeline and

stimulus severity in the current study. Although this was the case for fatigue, a significant association was observed between hemoglobin and timeline. Specifically, lower (poorer) hemoglobin levels were associated with the perception that CLL would last for a longer duration of time. Although most prior studies observed null effects, one previous report of chronic pain patients (Costa et al., 2016) also observed a covariation between greater stimulus severity (i.e., self-report pain) and perceptions of a more chronic illness timeline, potentially reflecting disease-specific differences in factors relevant to timeline perceptions. Furthermore, these results indicate that different stimuli within the same illness may differentially impact timeline (and other) illness perceptions. While hemoglobin was related to timeline perceptions, fatigue was not, perhaps indicating that somatic sensations unique to low hemoglobin (i.e., dizziness, lightheadedness, heart palpitations) confer unique information to mental representations. This may also account for the discrepant results for consequences and emotional responses, which were both associated with self-reported fatigue yet unassociated with hemoglobin.

Contrary to hypotheses, fatigue and hemoglobin were also unrelated to personal and treatment control at baseline, indicating that control perceptions may be influenced predominantly by other factors in CLL. Leventhal and colleagues (1980) theorized that, in addition to somatic stimuli and their severity, knowledge acquired through previous experiences with a stimulus also plays a central role in the development of mental representations. Interestingly, personal control had the lowest average score among all dimensions in the sample (3.65/10), while treatment control was among the highest (8.17/10). These findings indicate that patients have come to perceive that, while there is

little they can personally do to control CLL, treatment is at least temporarily helpful for their condition.

Pre-Treatment Findings:

Lymphocyte Count, Organ Enlargement, and Lymph Node Volume

Interestingly, pre-treatment lymphocyte count and organ enlargement were significantly associated with emotional responses but no other illness perceptions. These findings, in addition to the null effects of lymph node volume, may reflect low salience of these disease variables. Nonetheless, this raises the question of what other factors may account for the relation of lymphocyte count and organ enlargement to emotional responses. One plausible mechanism is the role of inflammatory cytokines such as interleukin-1B (IL-1B), tumor necrosis factor-alpha (TNF-a), and both interferon alpha (IFN-a), and gamma (IFN-g). Leukemic B-cells (a lymphocyte subtype) proliferate rapidly in CLL, accumulating in several sites including the blood, spleen, and liver, leading to elevated lymphocyte counts in the periphery as well as the occurrence of organ enlargement (Mentzer et al., 1987; Murakami & Shimizu, 2013; Woyach et al., 2014). These leukemic B-cells produce several inflammatory cytokines, including IL-1B, TNF-a, IFN-a, and IFN-g (Gallego et al., 2003; Kern, Quiney, Billard, & Kolb, 2008). Other work from our group has corroborated this association, documenting moderate-to-strong correlations between lymphocyte counts and inflammatory cytokines including TNF-a (r=.324), IL-10 (r=.300), and IL-16 (r=.576) in the context of relapsed/refractory CLL (Goyal et al., under review). These cytokines, in addition to facilitating CLL cell survival, have also been linked to mood and behavioral alterations in both human and animal

models (Dantzer, 2009; Pollak & Yirmiya, 2002). For example, patients with major depressive disorder exhibit several features of an inflammatory response, including elevated levels of cytokines and chemokines in peripheral blood and cerebrospinal fluid (Miller & Raison, 2016). Furthermore, direct administration of cytokines in medical samples show concurrent elevations in psychiatric symptoms including anxiety, irritability, and depression (Constant et al., 2005; Dantzer, 2009). Cumulatively, these factors suggest that one potential pathway by which elevated lymphocyte counts and organ enlargement impact emotional responses is through inflammatory processes. Future research will be needed to examine the potential mediating role of inflammatory cytokines in this relationship.

Longitudinal Illness Perception Change

In addition to the type and severity of the illness stimulus, Leventhal and colleagues postulated that *changes* to the stimulus are also integral to the development of illness perceptions and their change over time (Leventhal et al., 1998; Diefenbach & Leventhal, 1996). For example, an individual who develops a headache of similar intensity to prior experiences with the symptom may initially develop a benign illness perception. However, if the stimulus were to become more intense, the perception would be "updated" to incorporate this new information – presumably to a more negative variant than the original. In support of this hypothesis, several illness perceptions improved over the first 5-months of treatment, at a time when salient improvements to disease status were also occurring. Interestingly, total illness threat, consequences, identity, personal control, concern, and emotional responses all improved by Month 2,

then remained stable until Month 5. This indicates that, not only do illness perceptions change in the context of improving symptoms, they also do so relatively quickly. This finding adds to a growing literature indicating that illness perception change can occur on time-scales smaller than typically assessed in the literature (e.g., 6-month follow-ups and beyond), for example, even that of minutes or hours (Devcich, Ellis, Broadbent, Gamble, & Petrie, 2012).

It is also noteworthy that, while most illness perceptions improved by Month 2, treatment control was not improved relative to baseline until Month 5. While this could be the result of high baseline treatment control perceptions (8.17/10), it could also indicate that some illness perceptions "update" at different rates than others under the same circumstances. While there is a dearth of previous illness perception data to consider this finding, differential rates of improvement in other psychological variables have been reported. For example, Andersen and colleagues (2017) identified that, among surgically-treated breast cancer patients followed from diagnosis through 5 years, depressive symptoms improved and reached stability by 7 months following surgery, whereas cancer-specific stress improved through 12 months, with continued, slower rates of improvement thereafter. In the context of CLL, results suggest that stimulus change by 2 months may be of sufficient magnitude to shift several illness perceptions (i.e., total illness threat, consequences, identity, personal control, concern, and emotional responses), but more "data" is needed through 5 months to shift already high perceptions of treatment control.

Lastly, longitudinal patterns of how well one believes they understand CLL (coherence) departed from our hypothesis of general improvement over time. In fact,

coherence was the only dimension to become less favorable from baseline (8.30/10) to Month 2 (7.90/10), which was followed by an increase through Month 5 (8.08/10) to levels statistically equivalent to baseline and Month 2. The coherence dimension had the highest average score and smallest standard deviation (1.86) of all illness perceptions in the sample, indicating that participants felt strongly that they understood CLL. High coherence perceptions may also be reflective of the sociodemographic characteristics of the sample, which was largely affluent, educated, Caucasian (97%), and able to travel to Ohio State from across the country (average distance from home to OSU = 340 miles). These factors, in addition to the resourcefulness required to locate and access clinical trials of novel drug agents, may not be representative of the general CLL population. The observed declines in coherence could therefore reflect regression to the mean. However, no known studies have administered multiple illness perception assessments while patients initiate and receive an active treatment, relying instead on pre-post assessments following surgical procedures (Astin et al., 2006) or cardiac rehabilitation (Fischer et al. 2010; Janssen et al., 2013). It could be that coherence perceptions are in flux during active treatment, but that assessments of prior studies were insufficiently timed or spaced to detect effects. Future work will be needed to clarify longitudinal patterns of coherence perceptions both in and outside the context of active treatments.

Predicting Illness Perception Change:
The Role of Changes in the Illness Stimulus

While previous studies have linked illness stimuli to illness perceptions in cross-sectional designs, or documented changes in illness perceptions among those undergoing

presumed stimulus changes, no known studies have examined whether measured stimulus changes indeed account for variance in the illness perception changes which occur. Leventhal and colleague's emphasis on the relevance of illness stimulus changes to illness perception can also be observed in the inclusion of appraisal components in the original model (Figure 1). These pathways conceptualize how patients continuously reincorporate information about changes in the stimulus into all facets of self-regulation. For example, after implementation of a coping behavior (e.g., treatment), individuals appraise the efficacy of that behavior based on any changes to the stimulus that occur. The results of this appraisal then go on to influence other portions of the model, including future coping attempts and the mental representation of the threat itself. In support of Leventhal's SRM, we identified that, controlling for number of prior therapies, changes in both subjective fatigue and objective disease markers during the first 2- and 5-months of treatment were significant predictors of illness perception change.

Changes in self-reported fatigue were associated with the greatest number of illness perceptions (Summary Table 9), predicting changes in total illness threat, consequences, and identity at Month 2, and these same dimensions in addition to timeline and emotional responses at Month 5. Across all relationships, the direction of effects indicated that improvements in fatigue were associated with more favorable perceptions of CLL.

At the objective stimulus level, hemoglobin change predicted changes in identity and concern at Month 2, and changes in identity, total illness threat, and consequences at Month 5. Changes in lymph node volume were associated with changes in total illness threat at Month 2, and both total illness threat and concern at Month 5. Lymphocyte

count was associated with changes in identity at Month 5. Similar to fatigue, direction of effects indicated that improvements in hemoglobin, lymph node volume, and lymphocyte counts during treatment were associated with more favorable perceptions of CLL.

In addition to providing novel empirical support for theorized relationships between illness stimuli and illness perceptions, these findings also add complexity to our basic understanding of fundamental postulates of the SRM. For example, while Leventhal and colleagues theorized that illness stimuli and their change were broadly relevant to illness perceptions, our results indicate that changes in somatic characteristics of the stimulus may be more relevant to certain perceptions than others. For example, stimuli and their change, particularly those of fatigue and hemoglobin, were repeatedly linked to overall threat towards CLL, the perception of CLL-specific consequences and symptoms (identity), and emotional representations of CLL (emotional responses and concern). Stimulus changes were less consistently related to perceptions of how long CLL would last (timeline).

Similarly, personal control, treatment control, and coherence were not associated with changes in illness stimuli. In combination with Aim 1 data showing no significant associations between these perceptions and stimulus severity at baseline, results collectively suggest that stimulus severity and its change are less relevant to control and coherence than other perceptions. This lack of association is particularly noteworthy for treatment control, as it would be anticipated that improvements in somatic symptoms would be a primary source of information on which appraisals of the efficacy of treatment would be based. Although this could be a product of high baseline levels, it

could also indicate perceptions of treatment control in CLL are shaped by other factors such as objective feedback regarding treatment efficacy from physicians.

Strengths and Limitations

The current study has several strengths. First, it provides new knowledge of an understudied component of Leventhal's Self-Regulatory Model, i.e., the relationship between characteristics of the illness stimulus and corresponding illness perceptions. The methodology, including subjective, but most importantly, objective measurements of illness stimuli in a longitudinal design, provided a new understanding of the complex processes of change in patients' mental representations of illness. This expands upon a prior literature which has consisted primarily of cross-sectional designs and/or self-reported of illness stimuli, i.e., symptoms.

Furthermore, the low toxicity profile of the study drug (ibrutinib) allowed for ideal examination of changing illness stimuli, per se, rather than toxicities of treatment. Toxicities most common during receipt of ibrutinib are easy bruising/petechiae (61% of patients) and diarrhea (58% of patients), rather than the nausea, fatigue, neuropathy, and hair loss common to standard chemotherapies. The timing of assessments for the current study (Month 2 and Month 5) was also a methodological strength, corresponding appropriately to the most critical periods of change in underlying disease biology. Analysis of change by Month 2 provided an understanding of how illness perceptions develop during the most rapid changes in illness stimuli, while analysis at Month 5 captured effects as disease changes begin to stabilize. Lastly, as targeted therapies are poised for primary use in CLL and other cancers (Burger et al., 2015; D'Arcangelo &

Cappuzzo, 2013; Rehman, Silk, Kane, & Kaufman, 2016), replacing chemotherapy, the study is timely and provides the first known data documenting illness perception changes early in the course of targeted therapy.

Findings must also be considered in the context of limitations to the study. As discussed in Study 1, patients were engaged in treatment through the context of a clinical trial, which as a class of studies in general tend to underrepresent minorities and older adults (Eichhorst et al., 2009; Heller et al., 2014). Thus the demographic makeup of the current study in respect to age and race (mean age=64 years; 97% Caucasian) differs from that of national CLL samples (median age at diagnosis=71; 90% Caucasian; Miller et al., 2016; Shenoy et al., 2011). The sample participating was also affluent, educated, and able to travel to the study site from across the country, potentially lessening external validity. Relatedly, illness perceptions of patients treated at a university-affiliated comprehensive cancer center may differ from those of individuals treated in the community. Furthermore, while longitudinal, the single group, observational design precludes the ability to make causal assertions regarding the relationship between illness stimuli and illness perceptions.

It is also relevant to consider limitations to change scores which were used as independent variables for primary regression analyses. One critique for the use of change scores in social science research is that all self-report measurements contain some degree of error (e.g., due to misunderstanding instructions or questions, answering randomly, false-reporting) and thus a change score, which is calculated from two "imperfect" measurements, likely contains greater error than either score on its own (Dalecki & Willits, 1991; Gillespie & Streeter, 1994). Pendleton and colleagues (1979) also suggest

that change scores do not account for an individual's initial standing, or baseline measurement, which may be statistically relevant to the dependent variable or overall change. Lastly, it has been argued that the use of difference scores as independent variables (as done here) can produce a conservative statistical test and thus reduces the amount of overall explained variance observed (e.g., R^2 values; Edwards, 2001). Although there is no "perfect" method for circumventing limitations of change scores, one approach involves computing a "residualized change score," wherein a subject's Time 2 score is predicted by their Time 1 score, then subtracted from the actual Time 2 score – thus reflecting the difference between the observed and the predicted Time 2 scores. The appeal of this approach is that it "statistically controls" for an individual's Time 1 score within the change score itself (Dalecki & Willits, 1991).

Lastly, although the Brief Illness Perception Questionnaire (BIPQ) is considered the preferred method for measuring illness perceptions when time constraints and/or assessment burden prevent use of the longer form, critiques of the measure's validity have been made. French and colleagues (2011) have raised specific concerns regarding the questionnaire's content validity, arguing that the single item subscale approach used prevents complete assessment of certain illness perception dimensions. They suggest, for example, that the prompt for the identity item of the current BIPQ ("How much do you experience symptoms of your illness?") does not entirely capture the identity *construct*, defined as: "patients' ideas about the label, the nature of their condition (i.e. associated symptoms) and the links between these" (Weinman et al., 1996, p. 433). A "talk-aloud study" by van Oort and colleagues (2011) supported these concerns about content

validity, finding that participants had occasional difficulty accurately interpreting and responding to identity, personal control, emotional responses, and coherence items.

Conclusions and Future Directions

In summary, the current study provides new data regarding determinants of illness perceptions in patients with relapsed/refractory CLL. Findings provide empirical support for a fundamental postulate of Leventhal's Self-Regulatory Model that somatic characteristics of the illness stimulus and their change over time influence the development and progression of mental representations of illness. Results demonstrated that illness perceptions were concurrently associated with both subjective and objective illness stimuli at baseline and generally improved during the first 5-months of treatment when salient improvements to disease status were also occurring. Moreover, controlling for number of prior CLL therapies, changes in self-reported fatigue and objective disease markers accounted for significant portions of variance in illness perception change.

In addition to providing empirical support for basic assumptions of Leventhal's work, an understanding of the relationship between illness stimuli and illness perceptions emerged. First, the relationship between stimuli and perceptions was not uniform; different stimuli were related to different perceptions. As one example, lower hemoglobin was related to more chronic timeline perceptions, while fatigue was not, indicating that sensations unique to low hemoglobin (e.g., lightheadedness, heart palpitations) may convey different types of information to illness perceptions than fatigue. An important future direction will be investigation of why these disparate effects of illness stimuli occur. For example, it is feasible that other characteristics of a stimulus,

including its novelty, unpredictability, or variability, may "activate" certain dimensions of illness perception differently than others.

Furthermore, results indicated that illness perceptions are updated relatively quickly with stimulus improvements. Some stimulus improvements (i.e., hemoglobin and lymph node volume) continued through 5-months of treatment, yet the majority of illness perceptions improved by Month 2 and remained stable through Month 5. Future work may benefit from use of even shorter follow-up intervals, perhaps on the scale of weeks, to gain a more nuanced understanding of longitudinal patterns of illness perception change. Warranting an appropriate context, use of a measurement approach such as ecological momentary assessment (Moskowitz & Young, 2006) may also be worthwhile, and would allow for repeated measurements of illness stimuli and illness perceptions in real time.

Lastly, results indicated that somatic stimulus severity and changes may be more relevant to certain perceptions (i.e., consequences, identity, concern, emotional responses) than others (i.e., timeline, personal control, treatment control, coherence). An important line of research will involve the identification and study of other factors (e.g., communication with healthcare providers, disease specific knowledge) that may be influential to the development of illness perceptions. Moreover, while empirical focus on the role of somatic stimulus severity was a valuable and theoretically consistent first step, it is likely that stimuli interact with these other factors when influencing illness perceptions. For example, stimulus severity may be less concerning among patients informed by their physician that increases in severity are normative. Concurrent

examination of multiple determinants of illness perception and their interaction over time will be an important area of future research.

Chapter 8: General Discussion

A basic postulate of Leventhal's Self-Regulatory Model of Illness Behavior (SRM; 1980), which suggests that illness perceptions are influenced primarily by somatic characteristics of the illness stimulus (e.g., symptom severity), previous experiences with the stimulus (e.g., treatment), and changes in the stimulus over time, was tested. In Study 1, illness perceptions differed between three groups of CLL patients varying in symptom severity and prior treatment experiences: active surveillance, initiating a first treatment, and relapsed/refractory disease. While consequences, identity (symptoms), and illness concern were poorer among patients at each successive phase of treatment, perceptions of how well one understands CLL (coherence) and how long CLL will last (timeline) were poorest among those earliest in the trajectory (i.e., active surveillance). Patients initiating a first treatment believed more strongly that they personally could control their illness (personal control) and that CLL treatment would be helpful (treatment control). In Study 2, focusing on relapsed/refractory CLL patients initiating treatment, it was observed that illness perceptions covaried with subjective fatigue and objective disease markers at pre-treatment and generally improved during the first 5-months of treatment when substantial improvements to disease status were occurring. Moreover, controlling for number of prior CLL therapies, changes in subjective and objective stimuli which occurred during treatment accounted for significant portions of variance in illness perception change.

Leventhal, Brissette, & Leventhal (2003) have summarized their theoretical work regarding the role of illness stimuli and their change on illness perceptions:

> "At the heart of the [Self-Regulatory Model] is the proposition that representations are generated and shaped by the experience of disease biology. The pain, nausea, rashes … evoked by disease make powerful and at times, dominating contributions to the illness representation. And the greater the magnitude and rapidity of change of these somatic indicators, the greater their contribution to the representation of a health threat." (pp. 58)

Synthesizing results across studies, the most consistent evidence supporting the relationship between stimulus severity and illness perceptions was observed for the dimensions of consequences and identity (symptoms). In Study 1, patients perceived more consequences and symptoms at each successive phase of treatment, corresponding to a clinical picture of increasing stimulus severity as patients transition from surveillance to a first treatment and beyond (Levin et al., 2007; van den Broek et al., 2015; Pashos et al., 2013). In Study 2, consequences and identity were associated with fatigue and hemoglobin at pre-treatment, and also improved during the first 2-months of treatment when rapid changes to disease biology were occurring. Lastly, controlling for prior CLL therapies, changes in fatigue, hemoglobin, and lymphocyte count which occurred during treatment accounted for 2- and 5-month change in consequences and identity.

Synthesis of results from both studies yields more complex patterns of findings for illness concern. For example, in Study 1, CLL-specific concern was significantly greater at each successive phase of CLL treatment, with active surveillance patients reporting the lowest concern, followed by those initiating a first treatment, then those

with relapsed/refractory disease. Furthermore, in Study 2, improvements in lymph node volume and hemoglobin during the first 2- and 5-months of treatment were significant predictors of improvements in concern. However, contrary to Study 2 hypotheses, concern was not associated with stimuli at baseline. This could indicate that treatment experiences and stimulus changes are more relevant to concern in relapsed/refractory CLL than severity captured at a single time point. For example, as CLL patients transition from surveillance to a first treatment and beyond, they are experiencing (often repeatedly) disease progression and treatment failures. These "experiences with the stimulus", which are also theorized as central to the development of illness perceptions (Leventhal et al., 1980), are understandably concerning and likely contributed to the observed group differences. Likewise, as patients experience stimulus improvements during successful treatment (as observed in Study 2), they likely gain new, positive experiences and reassurance that their disease is on a more optimistic trajectory.

Emotional responses were also linked to CLL stimulus severity, particularly in Study 2, where they were associated with fatigue, lymphocyte count, and organ enlargement at baseline, and changes in fatigue over time. Nevertheless, despite differing in stimulus severity, the three groups in Study 1 did not differ in emotional responses. One potential explanation for this finding is the greater proportion of males (70%) in the relapsed/refractory group relative to surveillance (50%) and first-treatment groups (60%). As males may underreport negative emotions (Chaplin, 2015; Sigmon et al., 2005), it could be that the increased number of males in the relapsed/refractory group led to less reporting of negative emotions than would be observed with a different gender distribution. Similarly, the relapsed/refractory group was also significantly older (mean

age=64.08) than the surveillance (mean age=61.88) and first-treatment (mean age=59.03) groups. As older adults generally report fewer negative emotions (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000; Charles & Carstensen, 2010; Mather, 2012), the older age of the relapsed/refractory group may have led to equivalence between groups on negative emotional responses despite their differing in stimulus severity.

Perceptions of how long CLL would last (timeline) also demonstrated complex relationships with illness stimuli across studies. In Study 2, timeline was associated with hemoglobin at pre-treatment and 5-month changes in fatigue. However, in Study 1, timeline perceptions were most chronic among surveillance patients relative to those initiating a first or subsequent treatment. This pattern may stem from multiple factors. First, more chronic timeline perceptions among active surveillance patients (9.24/10) were "accurate" and consistent with disease-specific facts regarding the incurable nature of CLL. This indicates that timeline perceptions may be influenced in part by information regarding the objective chronicity of the condition, likely given to the patient by reputable authorities including healthcare providers. This link between objective chronicity and timeline perceptions has been observed in previous studies which document consistent differences in timeline perceptions between groups with acute vs. chronic health conditions (Broadbent et al., 2006; Moss-Morris et al., 2002). However, the less chronic timeline perceptions observed among those initiating a first (6.95/10) or subsequent (7.39/10) treatment indicated that some factor or set of factors led patients to perceive that CLL would last for a shorter duration of time. One such factor could have been characteristics of the study drug (i.e., ibrutinib), which was designated as a "breakthrough therapy" due to its superior clinical efficacy (Byrd et al., 2015). This or

similar information was likely transmitted to some patients via doctor-patient communication, the media, or other means, and potentially led some to perceive that CLL could be more effectively controlled or even cured. Moreover, the context of treatment could have also influenced timeline perceptions, as those initiating treatment were doing so at a National Cancer Institute-designated Comprehensive Cancer Center. Thus, while it appears that timeline perceptions are initially "calibrated" by objective disease-specific information, factors including a novel treatment approach or highly reputable treatment context may be able to shift timeline perceptions irrespective of objective chronicity.

Results also suggest that stimulus severity may be *less relevant* to perceptions of personal control, helpfulness of treatment (treatment control) and understanding of CLL (coherence). In Study 1, personal control and coherence did not vary across groups in a manner that would be expected on the basis of stimulus severity alone. Rather, personal control was highest among those initiating a first treatment and perceived understanding of CLL was poorest among those under active surveillance. While perceptions of the helpfulness of treatment were indeed poorer among relapsed/refractory patients relative to those initiating a first treatment, this was discussed in Study 1 as potentially reflecting experiential learning that occurs with time. Particularly in combination with Study 2 results, which demonstrated no associations between stimulus severity/stimulus change and control or coherence perceptions, these results collectively suggest that these dimensions may be primarily influence by other factors.

Similar to timeline, prior research suggests that factors including one's treatment context and disease-specific information may be particularly relevant to control and coherence perceptions. For example, Broadbent and colleagues (2006) contrasted illness

perceptions among patients from five health groups: diabetes, asthma, common cold, undiagnosed chest pain, and inpatients post-myocardial infarction (MI). Interestingly, personal control, treatment control, and coherence were highest among MI patients, which the authors attributed to their context of treatment. At the time, patients were receiving novel medical interventions and information regarding health behavior change, which likely led to enhanced control and coherence perceptions. Likewise, patients with the poorest scores on these dimensions were those with undiagnosed chest pain, who had not yet received a label for their symptoms or information regarding how they might be best controlled. Lastly, and in line with the current studies, authors observed no associations between angina severity and control or coherence perceptions in the MI group, bolstering their assertions that the treatment context and provision of disease-specific information were relevant to the increased control and coherence perceptions.

Regarding the specific role of disease knowledge and information provision, Husson and colleagues (2013) identified that myeloma and lymphoma patients (N=3080) who reported having received greater quality of disease-specific information also endorsed greater control and coherence perceptions. Relationships between information provision and other dimensions were not significant. Moreover, the direct administration of disease-specific information in the context of illness perception and other psychoeducational interventions has been associated with improvements to control and coherence in patients with MI, renal disease, prostate cancer, and head/neck cancer (Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009; Richardson, Tennant, Morton, & Broadbent, 2017; Traeger et al., 2013; Willems et al., 2017). Collectively, these results

suggest that factors including disease-specific information and, relatedly, an active treatment context may be more central to control and coherence than stimulus severity.

With this literature in mind, the patterns of observed group differences in Study 1 for personal control, treatment control, and coherence are more easily understood. Similar to the MI patients in Broadbent et al's report (2006; above), patients initiating a first CLL therapy were entering an active treatment context for the first time. Such an environment is likely associated with extensive information provision regarding methods for managing CLL, which conceivably influenced the elevated control perceptions among first-treatment patients relative to the other CLL groups. Although relapsed/refractory patients were also engaged in a treatment context, their control perceptions were likely tempered by knowledge acquired through previous experiences with treatment failure. The informational experiences associated with beginning a first or subsequent therapy also presumably influenced their elevated coherence perceptions relative to surveillance patients. Also likely relevant is the unique dissatisfaction with information provision commonly expressed by surveillance patients (Evans et al., 2012) discussed in Study 1.

Leventhal's Self-Regulatory Model: Revisited

Leventhal and colleagues have defined the illness stimulus as "somatic stimuli and general information about the disease threat" (pp. 380, Brownlee, Leventhal, & Leventhal, 2000; Diefenbach & Leventhal, 1996; Leventhal, Leventhal, & Contrada, 1998). Thus, illness perceptions can, theoretically, be activated and updated by two separate sources of information: 1.) stimuli at the concrete, somatic level, and 2.) general information acquired through previous experiences with the threat or interactions with

medical professionals. Synthesis of results from the current studies, as well as insights from the extant literature, suggest that these separate "components" of the illness stimulus may be more strongly linked to certain dimensions of illness perception than others. Displayed in Figure 8 is a modified self-regulatory model incorporating these new hypothesized relationships. While study results demonstrated repeated associations between stimulus severity/severity changes and consequences, identity (symptoms), concern, and emotional responses, stimulus severity was less consistently related to timeline, and completely unassociated with perceptions of personal control, helpfulness of treatment (treatment control) and understanding of CLL (coherence). Likewise, timeline, personal control, treatment control, and coherence exhibited patterns of group differences in Study 1 which were understandable when considering the broader literature linking factors such as information provision/disease knowledge and an active treatment context to these perceptions. It is also important to note that there is likely "cross-talk" between differing components of the illness stimulus, and that they conceivably interact with one another when influencing illness perceptions. Furthermore, bolded arrows in Figure 8 do not indicate that *no* relationships exist between, for example, somatic stimulus severity and coherence, but rather that certain facets of the stimulus may be more primary to certain perceptions than others.

This novel extension of Leventhal's SRM warrants replication and confirmation in other samples, as it has implications for research and practice. If certain components of the stimulus are more primary to certain perceptions than others, this offers investigators greater specificity when designing interventions or other empirical studies. For example, if a study aims to reduce cancer-specific distress via reductions in illness

concern or emotional responses, it may be more prudent to begin with interventions that reduce stimulus severity (e.g., progressive muscle relaxation) instead of the typical first step of providing educational information about the illness. Relatedly, when working with patients to reduce illness consequences and improve overall quality of life, it may be helpful in certain cases to begin with identification of strategies to reduce severity of physical symptoms, rather than restructuring beliefs about the long-term consequences of the condition. Lastly, if a clinician hopes to enhance medication adherence via improvements to perceptions of how helpful treatment will be (treatment control), it may be most efficient to identify and remedy gaps in disease knowledge rather than presuming that stimulus changes (i.e., "feeling better") will solely drive medication adherence.

In conclusion, two studies were conducted as empirical tests of a postulate of Leventhal's Self-Regulatory Model, which proposes that somatic characteristics of the illness stimulus and previous experiences with the stimulus influence illness perceptions. Results were largely in confirmation of Leventhal's postulate, though a more complex understanding of the relationship between illness stimuli and illness perceptions emerged. While somatic characteristics of the illness stimulus were associated with consequences, identity, concern, and emotional responses, they were less consistently related to timeline, personal control, treatment control, and coherence. Synthesis of results from the current studies and the extant literature suggests that while the former dimensions are linked to somatic stimulus experiences, the latter dimensions may be more influenced by the "informational" component of the stimulus. In light of these findings, a revised Self-Regulatory Model was offered, which outlines hypothetical primary relationships between separate facets of the illness stimulus (i.e., somatic vs. informational) and

different illness perceptions. Future studies are needed, particularly those that assess both facets of the stimulus and their interaction, in order to continue to foster a better understanding of the complex mechanisms underlying self-regulation.

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Appendix A: Tables

Table 1. Sociodemographic and Descriptive Characteristics for Study 1 CLL Participants by Treatment Group (N=330).

	Active Surveillance (N = 100)	First Treatment (N = 78)	Relapsed Refractory (N = 152)
Age (years), *M* (*SD)*	61.88 (8.33)[a]	59.03 (10.38)[a]	64.08 (10.79)[b]
Gender (Male)	50 (50%)[a]	47 (60%)[a]	107 (70%)[b]
Married (Yes)	84 (84%)	66 (85%)	131 (86%)
Race			
Caucasian	100 (100%)	76 (97%)	147 (97%)
African American	0 (0%)	1 (1%)	5 (3%)
Education			
High School/Technical School or Below	21 (21%)	21 (27%)	44 (29%)
Some College/College Graduate	40 (40%)	32 (41%)	58 (38%)
Some Graduate School/Graduate Degree	30 (30%)	25 (32%)	46 (30%)
Household Income (K)			
≤ 100	41 (41%)	39 (50%)	79 (52%)
>100	44 (44%)	34 (44%)	46 (31%)
Prefers Not to Answer/Unknown	15 (15%)	5 (6%)	27 (17%)

Note. Variables with group differences are denoted by superscripts. Similar superscripts in a row denote values that do not significantly differ. Dissimilar superscripts in a row denote values that significantly differ.

Table 2. Sociodemographic, Disease, Treatment, and General Health Characteristics for Study 2 Relapsed/Refractory CLL Patients (N=152)

Sociodemographic	M (SD)	N (%)
Age (years), *M* (SD)	64.08 (10.80)	
Gender (male)		107 (70%)
Married/Partnered (yes)		131 (86%)
Race		
Caucasian		147 (97%)
African-American		5 (3%)
Education		
High School/Technical School or Below		44 (29%)
Some College/College Graduate		58 (38%)
Some Graduate School/Graduate Degree		46 (30%)
Household income (K)		
≤ 100		79 (52%)
>100		46 (31%)
Prefers Not to Answer/Unknown		27 (17%)
Disease, Treatment, and General Health		
Partial deletion of chromosome 17p (present)		78 (51%)
Number of prior therapies	3.47 (2.61)	
Charlson Comorbidity Index	2.53 (0.99)	

Table 3. Baseline Descriptive Statistics and Intercorrelations for Illness Perception and CLL Illness Stimuli Variables in CLL patients (N=152).

Illness Perception	M (SD) or N (%)	Range	Intercorrelations				
			Fatigue	Lymph Volume	Hemoglobin	Lymphocyte Count	Organ Enlargement
Total Threat	37.67 (10.12)	8 - 59	.448**	.062	-.183*	.090	.193*
Consequences	4.84 (2.89)	0 - 10	.480**	.067	-.128	.011	.066
Identity	4.46 (2.81)	0 - 10	.540**	.103	-.225**	.048	-.035
Timeline	7.39 (2.78)	0 - 10	-.017	.026	-.196*	.089	.110
Personal Control	3.65 (2.77)	0 - 10	-.106	-.024	.160	-.046	-.186*
Treatment Control	8.17 (1.87)	2 - 10	-.127	.028	-.008	.027	-.017
Concern	7.44 (2.77)	0 - 10	-.012	.040	.078	.005	.093
Coherence	8.30 (1.86)	0 - 10	.034	.158	-.100	.085	-.098
Emotional Responses	3.76 (2.92)	0 - 10	.368**	.063	-.106	.208*	.227**
CLL Illness Stimuli							
Fatigue (FSI)	16.15 (15.59)	0 - 60	1				
Lymph Node Volume (cm^2)	68.14 (82.83)	1.14 - 732.17	-.006	1			
Hemoglobin (g/dL)	10.87 (2.10)	6.5 - 15.4	-.274**	-.084	1		
Lymphocyte Count (10^9/L)	58.37 (58.26)	.30 - 305.7	.248**	.064	-.272**	1	
Organ Enlargement (present)	111 (73%)	--	.143	.061	.009	.133	1

* Correlation is significant at the .05 level, two tailed.

** Correlation is significant at the .01 level, two tailed.

Table 4. Intercorrelations between CLL illness stimuli and illness perceptions at Month 2 and Month 5 for CLL patients (N=152).

	Month 2								
	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Fatigue (FSI)	.517**	.471**	.670**	-.049	-.219**	-.254**	.121	-.092	.415**
Lymph Node Volume (cm^s)	-.079	.023	-.080	-.165	.022	.056	-.014	.050	-.014
Hemoglobin (g/dL)	-.161*	-.223**	-.239**	-.141	-.007	.055	-.014	-.149	-.112
Lymphocyte Count (mcL)	.034	.053	.096	.023	.090	.077	.004	.200*	.131
Organ Enlargement (present)	.024	.048	.062	-.069	-.047	-.036	.049	-.031	.025
	Month 5								
	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Fatigue (FSI)	.575**	.515**	.498**	.132	-.302**	-.286**	.104	-.235**	.500**
Lymph Node Volume (cm^s)	-.020	.072	.013	-.154	-.046	.-003	-.064	.126	.033
Hemoglobin (g/dL)	-.351**	-.390**	-.283**	-.251**	.197*	.100	-.240**	-.001	-.081
Lymphocyte Count (mcL)	.222*	.173*	.106	.110	-.139	-.058	.129	.104	.144
Organ Enlargement (present)	.089	.137	-.004	.037	-.163	-.015	.001	.024	.081

* Coefficient is significant at the .05 level, two tailed.

** Coefficient is significant at the .01 level, two tailed.

Table 5. Illness perception differences by baseline organ enlargement status for CLL patients (N=152).

	No Enlargement (N=35; 27%) M (SD)	Enlargement (N=111; 73%) M (SD)	*p*
Total Threat	34.71 (8.46)	38.18 (10.55)	.079
Consequences	4.43 (2.50)	4.79 (2.94)	.513
Identity	4.60 (2.61)	4.27 (2.85)	.544
Timeline	6.80 (2.91)	7.62 (2.68)	.128
Personal Control	4.43 (2.62)	3.41 (2.78)	.060
Treatment Control	8.14 (1.73)	8.20 (1.91)	.879
Concern	7.00 (2.59)	7.51 (2.83)	.341
Coherence	8.34 (1.61)	8.22 (1.95)	.728
Emotional Responses	2.80 (2.36)	3.95 (2.99)	.039*

* Group difference is significant at the .05 level, two tailed.
** Group difference is significant at the .01 level, two tailed.

Table 6. Illness perception and illness stimulus change over time for CLL patients (N=152).

Illness Perception	Baseline M (SD)	Month 2 M (SD)	Month 5 M (SD)	*F*	*p*
Total Threat	37.67 (10.12)[a]	32.20 (9.87)[b]	31.16 (10.98)[b]	32.63	.000**
Consequences	4.84 (2.89)[a]	3.66 (2.65)[b]	3.55 (2.79)[b]	16.55	.000**
Identity	4.46 (2.81)[a]	3.20 (2.62)[b]	2.96 (2.40)[b]	19.64	.000**
Timeline	7.39 (2.78)[a]	7.91 (2.63)[a]	7.92 (2.58)[a]	2.82	.070
Personal Control	3.65 (2.77)[a]	4.57 (2.97)[b]	4.82 (3.14)[b]	11.43	.000**
Treatment Control	8.17 (1.87)[a]	8.49 (1.69)[a]	8.85 (1.45)[b]	9.03	.000**
Concern	7.44 (2.77)[a]	6.33 (3.14)[b]	6.28 (3.13)[b]	13.63	.000**
Coherence	8.30 (1.86)[a]	7.97 (1.95)[b]	8.08 (1.91)[ab]	3.64	.031*
Emotional Responses	3.76 (2.92)[a]	2.29 (2.38)[b]	2.44 (2.73)[b]	23.25	.000**
Illness Stimulus					
Fatigue (FSI)	16.15 (15.59)[a]	10.77 (13.42)[b]	9.70 (13.11)[b]	16.26	.000**
Lymph Volume (cm^2)	68.14 (82.83)[a]	29.26 (48.70)[b]	20.72 (34.76)[c]	110.41	.000**
Hemoglobin (g/dL)	10.87 (2.10)[a]	11.62 (1.88)[b]	12.42 (1.80)[c]	59.52	.000**
Lymphocyte Count (mcL)	58.37 (58.26)[a]	82.83 (87.03)[b]	48.09 (48.28)[a]	17.46	.000**

* F-test is significant at the .05 level, two tailed.
** F-test is significant at the .01 level, two tailed.
[a,b,c] Similar superscripts in a row denote values that do not significantly differ. Dissimilar superscripts in a row denote values that significantly differ.

Table 7. Number of patients in each organ enlargement group at Month 2 and Month 5 for CLL patients (N=152).

	Month 2 N(%)	Month 5 N(%)
Group 1: Organ enlargement present at baseline, absent at follow-up	20 (13%)	28 (18%)
Group 2: Organ enlargement present at both time points	87 (57%)	72 (48%)
Group 3: Organ enlargement absent at both time points	35 (23%)	27 (18%)
Group 4: Organ enlargement absent at baseline, present at follow-up	0 (0%)	3 (2%)
Deceased/Off Study	6 (4%)	17 (11%)
Physical exam not recorded	4 (3%)	5 (3%)
Total	152 (100%)	152 (100%)

Note. At baseline, 111 patients (73%) displayed evidence of enlargement, while 35 (27%) did not.

Table 8. Intercorrelations between candidate control variables and illness perceptions for Aim 3 analyses

	Month 2								
	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Age	.024	-.020	.078	-.024	-.011	-.029	.006	-.009	-.111
Number of Prior Therapies	.039	.154	.168	.004	-.071	.023	-.126	-.033	-.026
Charlson Comorbidity Index	.056	-.011	.078	-.021	-.033	-.131	-.078	.032	.114
Del17p	.060	-.017	.038	.045	-.105	-.025	-.064	-.053	.048
	Month 5								
	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Age	.010	-.006	.048	.037	-.031	.112	.071	.027	-.157
Number of Prior Therapies	.224*	.284**	.235**	.007	-.097	-.055	.059	-.099	.114
Charlson Comorbidity Index	.105	.056	.085	.061	-.062	-.081	-.032	-.078	.037
Del17p	.099	.050	.068	.079	-.012	.128	.014	-.118	.021

* Coefficient is significant at the .05 level, two tailed.

** Coefficient is significant at the .01 level, two tailed.

Table 9. Summary of significant Aim 3 associations between illness stimulus and illness perception change at Month 2 and Month 5 for CLL patients (N=152).

Illness Stimulus	**Illness Perceptions Associated with Stimulus Change at Month 2**	**Illness Perceptions Associated with Stimulus Change at Month 5**
Fatigue	Total illness threat, consequences, identity	Total illness threat, consequences, identity, timeline, emotional responses
Lymph Node Volume	Total illness threat	Total illness threat, concern
Lymphocyte Count		Identity
Hemoglobin	Identity, concern	Identity, total illness threat, consequences

Table 10. Change in fatigue predicting residual change from baseline to Month 2 and Month 5 in illness perception dimensions for CLL patients (N=152).

	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Final Model: Predicting 2-month IP									
Baseline illness perception	.571**	.556**	.518**	.528**	.523**	.514**	.507**	.665**	.495**
2-month change in fatigue	.234**	.160*	.314**	.033	-.141	-.028	.063	-.008	.092
$R^2\Delta$ through including fatigue	**.052**	**.024**	**.090**	.001	.020	.001	.004	.000	.008
Final Adjusted R^2	.308	.280	.260	.270	.346	.256	.251	.434	.213
Final Model: Predicting 5-month IP									
Baseline illness perception	.552**	.480**	.559**	.445**	.425**	.418**	.475**	.459**	.547**
5-month change in fatigue	.299**	.238**	.380**	.211**	-.103	.014	.084	.120	.157*
$R^2\Delta$ through including fatigue	**.083**	**.051**	**.111**	**.044**	.011	.000	.007	.014	**.024**
Final Adjusted R^2	.331	.252	.277	.216	.181	.161	.220	.190	.279

* Coefficient is significant at the .05 level, two tailed.
** Coefficient is significant at the .01 level, two tailed.
Note. Significant $R^2\Delta$ values are bolded. Number of prior therapies was included as a covariate for regression models predicting total illness threat, consequences, and identity at Month 5.

Table 11. Change in lymph node volume predicting residual change from baseline to Month 2 and Month 5 in illness perception dimensions for CLL patients (N=152).

	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Final Model: Predicting 2-month IP									
Baseline illness perception	.539**	.526**	.423**	.492**	.535**	.518**	.530**	.657**	.478**
2-month change in lymph node volume	.147*	.024	.119	.034	-.065	-.110	.122	.041	.078
$R^2\Delta$ through including lymph node volume	**.022**	.001	.014	.001	.004	.012	.015	.002	.006
Final Adjusted R^2	.292	.266	.170	.230	.358	.264	.282	.420	.218
Final Model: Predicting 5-month IP									
Baseline illness perception	.505**	.436**	.401**	.402**	.412**	.420**	.508**	.413**	.514**
5-month change in lymph node volume	.211**	.061	.132	.161	.006	-.140	.216**	-.068	.111
$R^2\Delta$ through including lymph node volume	**.044**	.004	.017	.026	.000	.020	**.046**	.005	.012
Final Adjusted R^2	.297	.220	.188	.162	.156	.174	.275	.168	.262

* Coefficient is significant at the .05 level, two tailed.

** Coefficient is significant at the .01 level, two tailed.

Note. Significant $R^2\Delta$ values are bolded. Number of prior therapies was included as a covariate for regression models predicting total illness threat, consequences, and identity at Month 5.

Table 12. Change in lymphocyte (WBC) count predicting residual change from baseline to Month 2 and Month 5 in illness perception dimensions for CLL patients (N=152).

	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Final Model: Predicting 2-month IP									
Baseline illness perception	.534**	.513**	.418**	.506**	.544**	.522**	.514**	.667**	.488**
2-month change in lymphocyte count	.053	.109	.072	-.041	-.026	-.007	-.013	.096	.101
$R^2\Delta$ through including lymphocyte count	.004	.012	.005	.002	.001	.000	.000	.009	.026
Final Adjusted R^2	.283	.262	.171	.244	.354	.262	.254	.437	.251
Final Model: Predicting 5-month IP									
Baseline illness perception	.475**	.404**	.389**	.416**	.427**	.401**	.474**	.435**	.524**
5-month change in lymphocyte count	.126	.146	.168*	.133	-.049	-.064	.007	.111	.050
$R^2\Delta$ through including lymphocyte count	.016	.021	**.028**	.017	.002	.004	.000	.012	.002
Final Adjusted R^2	.266	.222	.194	.185	.173	.157	.225	.188	.265

* Coefficient is significant at the .05 level, two tailed.
** Coefficient is significant at the .01 level, two tailed.
Note. Significant $R^2\Delta$ values are bolded. Number of prior therapies was included as a covariate for regression models predicting total illness threat, consequences, and identity at Month 5.

Table 13. Change in hemoglobin predicting residual change from baseline to Month 2 and Month 5 in illness perception dimensions for CLL patients (N=152).

	Total Threat	Consequences	Identity	Timeline	Personal Control	Treatment Control	Concern	Coherence	Emotional Responses
Final Model: Predicting 2-month IP									
Baseline illness perception	.535**	.510**	.431**	.500**	.527**	.524**	.517**	.675**	.486**
2-month change in hemoglobin	-.117	-.100	-.240**	-.001	-.017	.012	-.158*	-.165	-.061
$R^2\Delta$ through including hemoglobin	.014	.010	**.057**	.000	.000	.000	**.025**	.027	.004
Final Adjusted R^2	.279	.256	.218	.250	.333	.265	.288	.452	.225
Final Model: Predicting 5-month IP									
Baseline illness perception	.512**	.436**	.412**	.442**	.426**	.395**	.467**	.427**	.531**
5-month change in hemoglobin	-.247**	-.267**	-.262**	-.110	.130	.101	-.094	.034	-.070
$R^2\Delta$ through including hemoglobin	**.059**	**.068**	**.065**	.012	.017	.010	.009	.001	.005
Final Adjusted R^2	.307	.266	.225	.179	.179	.161	.217	.173	.267

* Coefficient is significant at the .05 level, two tailed.

** Coefficient is significant at the .01 level, two tailed.

Note. Significant $R^2\Delta$ values are bolded. Number of prior therapies was included as a covariate for regression models predicting total illness threat, consequences, and identity at Month 5.

Table 14. Supplementary summary of relationships between greater symptom severity and illness perceptions in cross-sectional studies (N=14).

Study, Sample, and Severity Measure	Illness Perception Dimension								
	Consequences	Identity	Emotional Responses	Personal Control	Treatment Control	Coherence	Timeline	Concern	Total Illness Threat
Artom et al., 2017; Inflammatory bowel disease (N=182); Subjective; IBD-Fatigue Scale	--	--	--	--	--	--	--	--	Positive
Chilcot et al., 2016; Chronic kidney disease (N=174); Subjective; Chalder Fatigue Questionnaire	--	--	--	--	--	--	--	--	Positive
Chisari & Chilcot, 2017; Vulvodynia (N=335); Subjective; Numeric Pain Rating Scale	Positive	Positive	Positive	Negative	Negative	Negative	NS	--	--
Costa et al., 2015; Chronic pain (N=200); Subjective; 5-point rating scale	Positive	Positive	Positive	Negative	Negative	Negative	Positive	Positive	--
Dalbeth et al., 2011; Gout (N=142); Subjective/Objective; Health Assessment Questionnaire, Serum urate, Number of tophi, Flare frequency	Positive	Positive	Positive	Negative	Negative	NS	NS	Positive	--
De Gucht, 2015; Inflammatory bowel disease (N=123); Subjective; Rome III Severity Criteria	Positive	Positive	Positive	NS	NS	NS	NS	--	--
Edelstein et al., 2012; Osteoporosis (N=202); Objective; Number of fractures	Positive	Positive	Positive	Negative	Negative	--	NS	--	--
Greco et al., 2015; Cardiovascular Disease (N=75); Objective; Left ventricular ejection fraction	--	--	--	--	--	--	--	--	Positive
Knowles et al., 2016; Osteoarthritis (N=120); Subjective; Osteoarthritis Index	--	--	--	--	--	--	--	--	Positive
Knowles et al., 2017; Inflammatory Bowel Disease (N=150); Subjective; Health Perceptions Questionnaire	--	--	--	--	--	--	--	--	Positive

Leonhart et al., 2016; Breast Cancer (N=255); Subjective; Somatic Symptom Severity Scale	--	--	--	--	--	--	--	--	Positive
Nordbø et al., 2017; Psoriasis (N=942); Subjective; Psoriasis Severity	Positive	Positive	Positive	--	--	--	--	--	--
Pretorius et al., 2014; Overactive Bladder (N=41); Subjective; Overactive Bladder Questionnaire	Positive	--	--	Negative	Negative	--	--	--	Positive
Zhang et al., 2016, Crohn's Disease (N=159); Subjective; Crohn's Disease Activity Index	--	--	--	--	--	--	--	--	Positive

**Note*. Higher scores on consequences, identity, emotional responses, and concern are worse. Higher scores on coherence, personal control, and treatment control are better. Higher timeline scores reflect perception of a more chronic illness timeline.
"--" = not reported.
"NS" = nonsignificant.

Table 15. Supplementary summary of relationships between symptom change and/or time and illness perception change in longitudinal studies (N=9)

Study, Sample, Context	Illness Perception Dimension								
	Consequences	Identity	Emotional Responses	Personal Control	Treatment Control	Coherence	Timeline	Concern	Total Illness Threat
Astin et al., 2006; Coronary heart disease (N=117); Symptom improvement over 8-months	Improved	Improved	--	Decreased	Decreased	--	More chronic	--	--
Bijsterbosh et al., 2009; Osteoarthritis (N=241); Natural change over 6-years	No change	No change	Improved	Decreased	No change	Improved	More chronic	--	--
Dempster et al., 2010; Esophageal cancer (N=189); Natural change over 1-year	Improved	Improved	--	No change	Decreased	No change	No change	--	
Fischer et al., 2010; Chronic obstructive pulmonary disease (N=87); Symptom improvement over 3-months	Improved	No change	No change	Improved	No change	No change	No change	--	--
Foster et al., 2008; Chronic low back pain (N=1591); Symptom improvement over 6-months	Improved	Improved	Improved	Improved	Improved	No change	No change	--	--
Janssen et al., 2013; Cardiac Rehabilitation Participants (N=158); Symptom improvement over 3-months	Improved	Improved	Improved	No change	Improved	Improved	No change	--	--
Lawson et al. 2008; Diabetes (N=158); Natural change over 2 years	No change	No change	Improved	No change	No change	Improved	No change	--	--
Rutter & Rutter, 2007; Irritable Bowel Syndrome (N=42); Symptom stability over 1-year	No change	No change	--	No change	No change	--	No change	--	--
Tasmoc et al, 2013; Chronic kidney disease (N=81); Natural change over 6-years	Improved	No change	Improved	No change	Improved	Improved	More chronic	--	

Note. Higher scores on consequences, identity, emotional responses, and concern are worse. Higher scores on coherence, personal control, and treatment control are better. Higher timeline scores reflect perception of a more chronic illness timeline.
"--" = not reported.

Table 16. Supplementary post-hoc comparisons (Tukey's Procedure) of illness perceptions between CLL treatment groups (Study 1; N=330).

Illness Perception Dimension	**Mean Difference Between Groups**		
	Active Surveillance vs. First Treatment	First Treatment vs. Relapsed/Refractory	Active Surveillance vs. Relapsed/Refractory
Identity	1.14**	1.36**	2.5**
Consequences	1.29**	.82*	2.1**
Concern	1.19**	.86*	2.06**
Coherence	.92**	.07	.99**
Personal Control	1.69**	1.36**	.33
Timeline	2.29**	.44	1.85**
Emotional Responses	.67	.15	.52

* Group difference is significant at the .05 level, two tailed.

** Group difference is significant at the .01 level, two tailed.

Note. Treatment control was contrasted using an independent sample's t-test and thus not included above.

Appendix B: Figures

Figure 1. Leventhal's Self-Regulatory Model of Illness Behavior (Adapted from Hagger & Orbell, 2003).

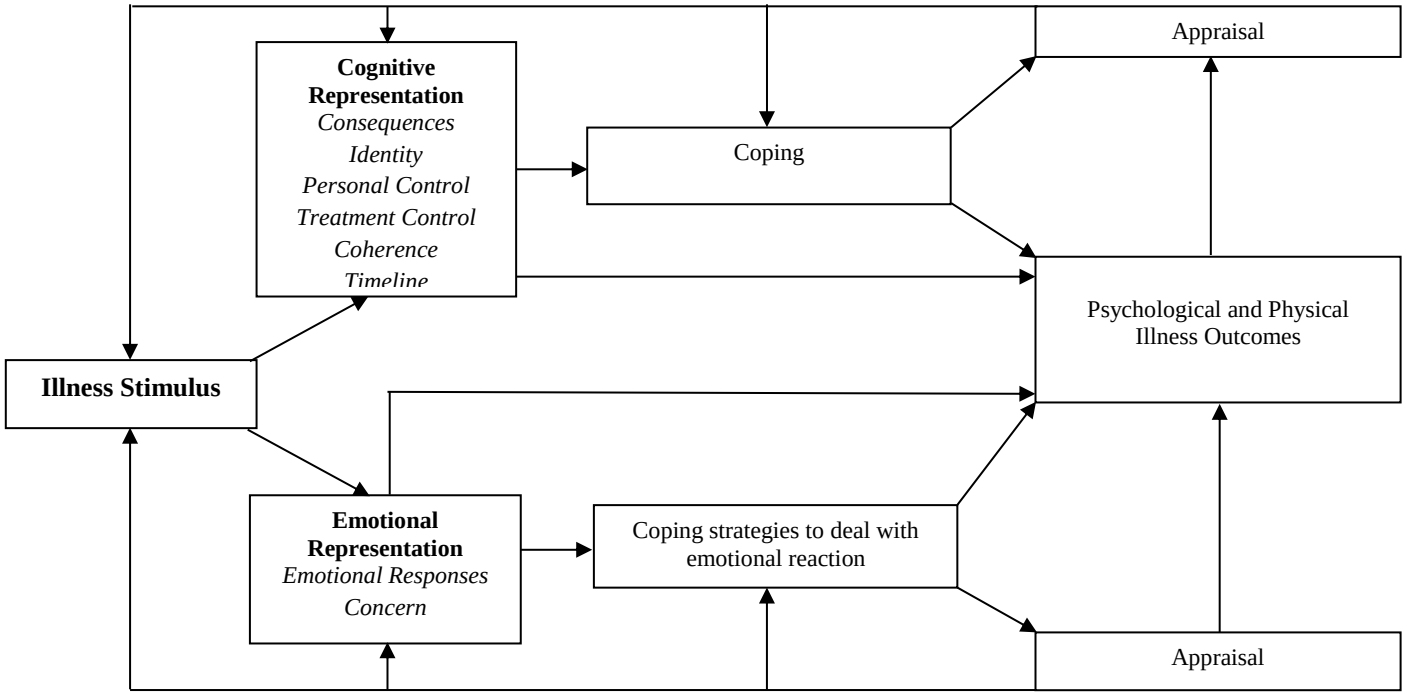


Figure 2. Lymphocytosis change-point in relapsed/refractory sample (Weiss et al., under review; N=152)

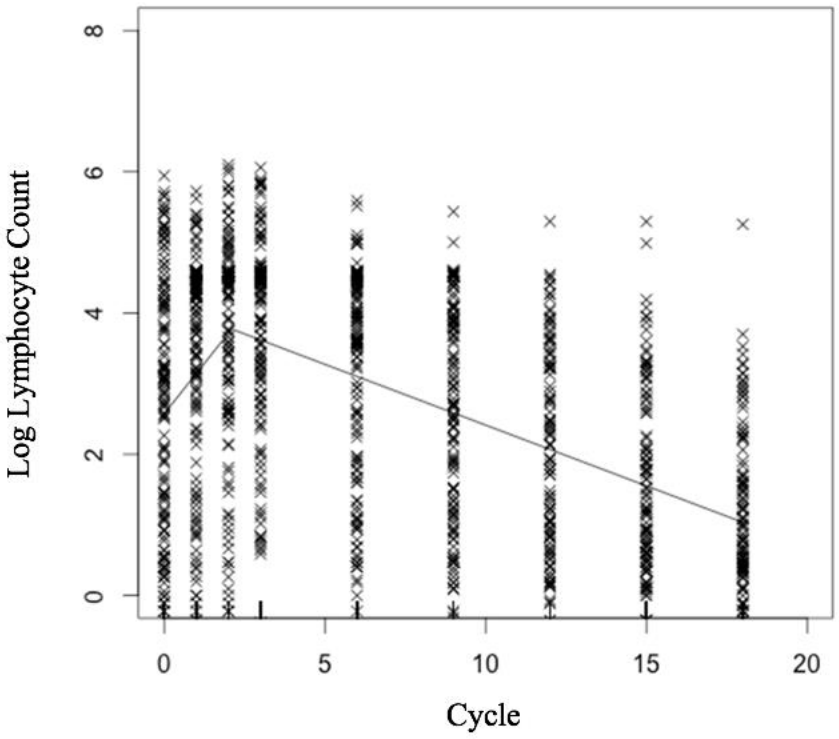


Figure 3. Study 1 Conceptual Diagram: Comparison of Illness Perceptions by CLL Group.

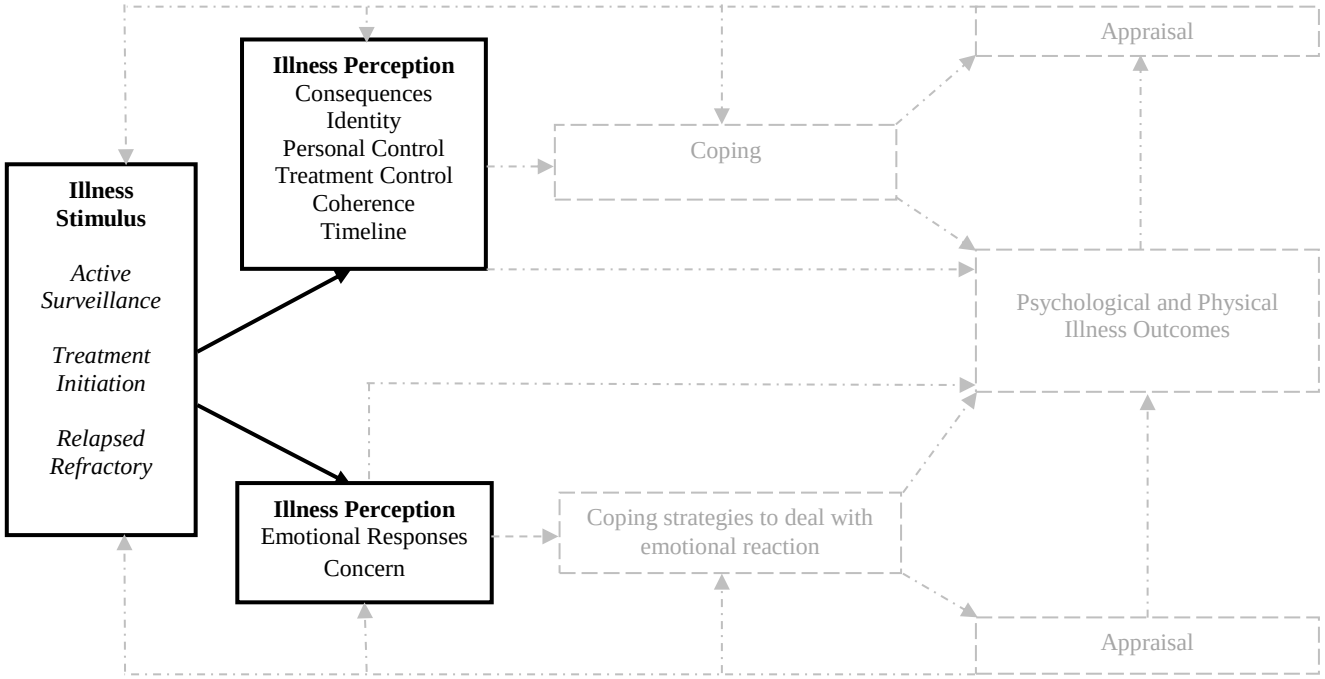


Figure 4. Study 2 Conceptual Diagram: Pre-Treatment Relationships Between CLL Illness Stimuli and Illness Perceptions.

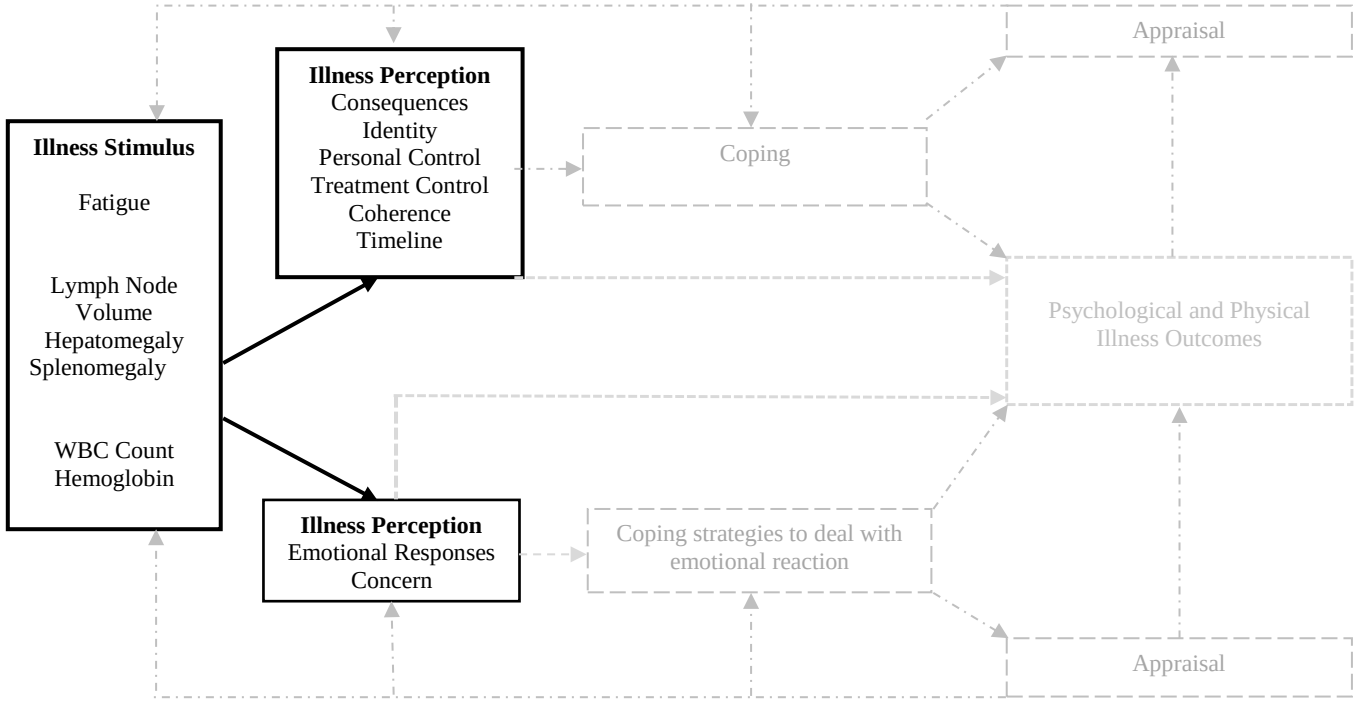


Figure 5. Study 2 Conceptual Diagram: Changes in Illness Stimuli Predicting Illness Perception Change.

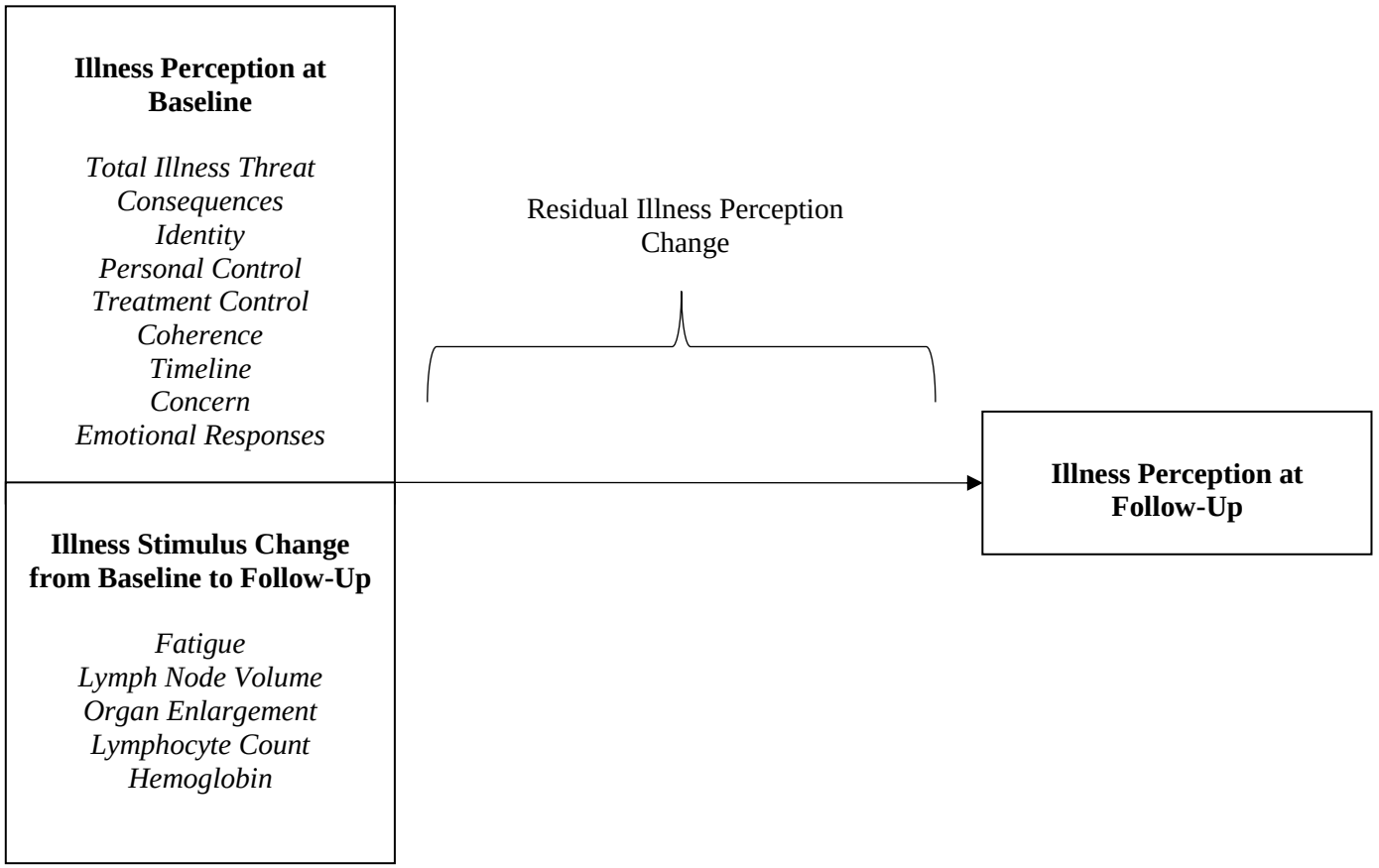
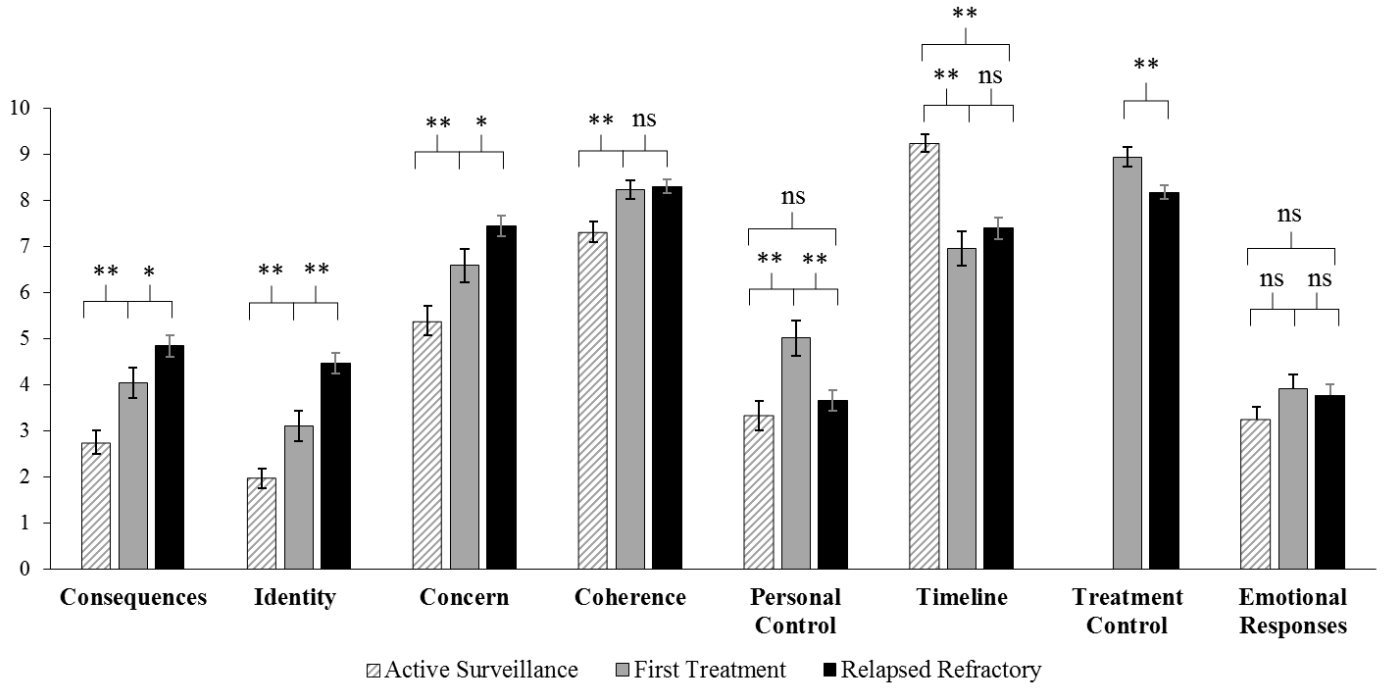


Figure 6. Illness Perception Differences by CLL Treatment Group (Study 1; N=330).



Note. Error bars denote standard errors of the group mean. The treatment control item was not administered to active surveillance patients. * = $p < .05$, ** = $p < .01$

Figure 7. Cumulative data availability and attrition for Study 2 relapsed/refractory CLL participants at baseline, Month 2, and Month 5

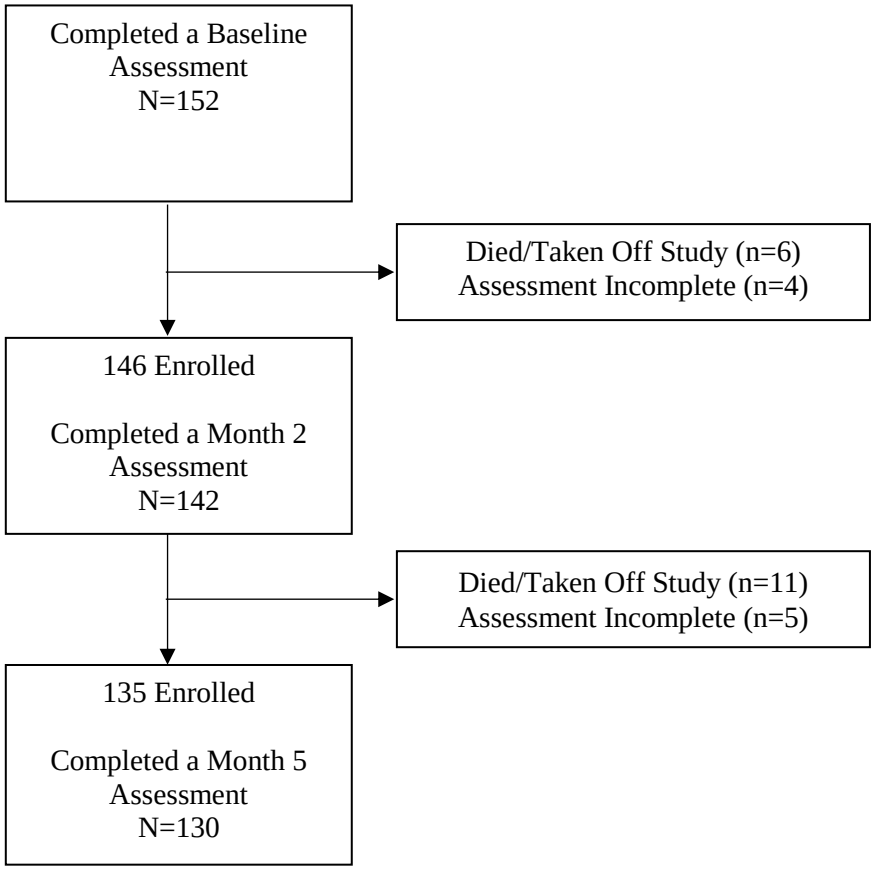
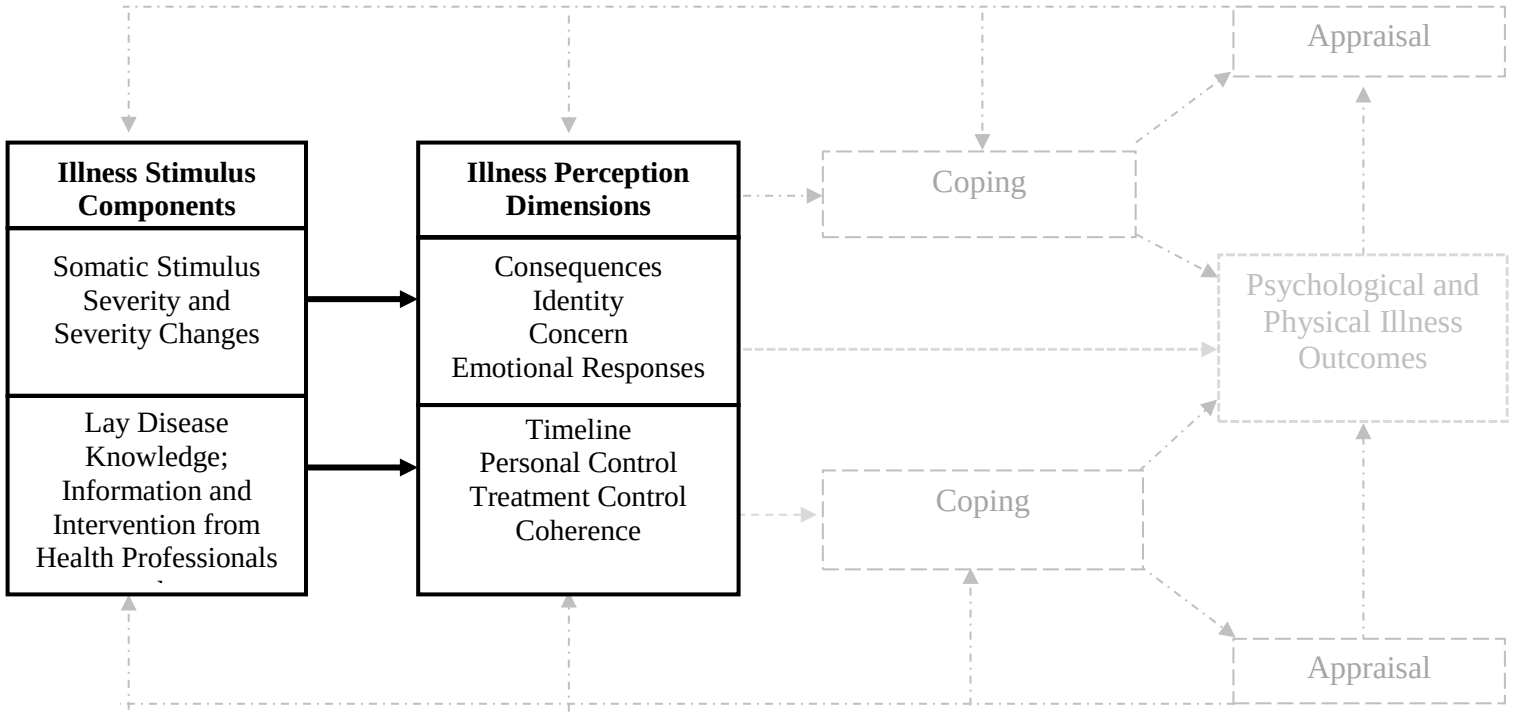


Figure 8. Modified Self-Regulatory Model incorporating separate components of the illness stimulus and their hypothesized primary relationships with separate illness perception dimensions



Appendix C: Measures

Subject ID

Assessment

Sociodemographics
CLL II Study
Page 1 of 2

Current date: ☐☐ / ☐☐ / ☐☐☐☐ **Birth year:** ☐☐☐☐

Home zip code: ☐☐☐☐☐

Gender:

O Male O Female

What is your ethnicity?

O Latina/Latino/Hispanic ancestry O Not Hispanic

What is your racial/ethnic group?(Choose yes or no for each; you may choose yes for more than one.)

Caucasian/White	O Yes	O No
African-American/Black	O Yes	O No
Asian	O Yes	O No
American Indian/Alaskan Native	O Yes	O No
Native Hawaiian/Other Pacific Islander	O Yes	O No
Other: _____	O Yes	O No

Have you ever been or are you currently married?

O Single, never married
O Currently married
O Not married, but in a relationship with significant other
O Separated or divorced
O Widowed

Are you currently living with a romantic partner?

O Yes O No

How long have you been married? If you are living with a romantic partner, how long have you been living together? (Code XX if not applicable; data code 99999).

☐☐ Years

How many individuals are living in your household? ☐☐

How many children under the age of 18 are living in your home? ☐☐

What is the highest level of formal education that you have completed?

O 8th grade or less
O Some high school
O Completed high school/GED
O Technical, vocational, or certificate program
O Some college (no degree)
O Associate's degree
O Bachelor's degree
O Some graduate school
O Master's degree
O Doctoral degree (MD, Phd, JD)

What is your current job status?

O Employed full-time
O Employed part-time
O Homemaker, raising children, care of others
O Disabled
O Temporarily unemployed, seeking employment
O Retired
O Retired, working part or full time
O Other _____

25800

Subject ID

Assessment

Sociodemographics
CLL II Study

On average, how many hours per week did you work for pay in the last month? (Code XX if not employed; data code 99999).

hours/week

If you work for pay, how many days did you take sick days or time off because of physical health problems since your cancer diagnosis? (Code XXXX if not employed; data code 99999.)

days

If you work for pay, how many days did you take sick days or time off because of emotional health problems since your cancer diagnosis? (Code XX if not employed; data code 99999.)

days

What is your occupation? If not currently employed, what was your occupation at your last full time job?

- O Homemaker
- O Major professional, executive or proprietor (e.g., MD or PhD level)
- O Lesser professional, manager or proprietors of medium-sized concern (MA or MS level)
- O Administrative personnel of large concern, owner of small business (e.g., teacher, nurse)
- O Assistant manager, owner of little business
- O Technician (high tech type)
- O Clerical or sales person
- O Skilled crafts person
- O Semi-skilled operative (e.g., school bus driver)
- O Unskilled labor

How important is your occupation or continuing to work to your well-being? If retired, disabled, or unemployed, how important was your occupation or continuing to work to your well-being?

- O Not at all important
- O Not very important
- O Somewhat important
- O Moderately important
- O Very important

What are/were your household (family) gross wages or income last year (pre-tax)?

- O Less than $15,000
- O $15,001 - $25,000
- O $25,001 - $35,000
- O $35,001 - $50,000
- O $50,001 - $75,000
- O $75,001 - $100,000
- O $100,001 - $150,000
- O $150,001 - $200,000
- O $200,001 - $250,000
- O More than $250,000
- O I don't know.
- O I prefer not to answer.

25800

Subject ID

Your Perception of CLL

BIPQ-*CLL Study*

Assesment

For each of the following, fill in the one number that best corresponds to your views.

1. How much does your illness affect your life?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

No affect at all — **Severly affects my life**

2. How long do you think your illness will continue?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

A very short time — **Forever**

3. How much control do you feel you have over your illness?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Absolutely no control — **Extreme amount of control**

4. How much do you think treatment can help your illness?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Not at all — **Extremely helpful**

5. How much do you experience symptoms from your illness?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

No symptoms at all — **Many severe symptoms**

6. How concerned are you about your illness?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Not at all concerned — **Extremely concerned**

7. How well do you understand your illness?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Don't understand at all — **Understand very clearly**

8. How much does your illness affect you emotionally (e.g. makes you angy, sad, scared, upset, depressed)?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Not at all affected emotionally — **Extremely affected emotionally**

9. Please list in rank-order the three most important factors that you believe caused your illness:

a. _____ b. _____ c. _____

Draft

Subject ID

Assessment

Signs of Fatigue
CLL II Study - FSI-R

For each of the following, fill in the one number that best indicates how that item applies to you.

1. Rate how much, in the past week, fatigue interfered with **your enjoyment of life:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

2. Rate how much, in the past week, fatigue interfered with your **general level of activity:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

3. Rate how much, in the past week, fatigue interfered with your **ability to bathe and dress yourself:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

4. Rate how much, in the past week, fatigue interfered with your **normal work activity** (includes both work outside the home and housework):

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

5. Rate how much, in the past week, fatigue interfered with your **ability to concentrate:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

6. Rate how much, in the past week, fatigue interfered with your **relations with other people:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

7. Rate how much, in the past week, fatigue interfered with your **mood:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
No interference										**Extreme Interference**

41541

Subject ID

Assessment

Feelings in the Past Month

CLL II Study - BDI-II

Instructions: This questionnaire consists of 23 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past month, including today.** Fill in the Circle beside the statement you have picked. If several statements in the group seem to apply equally well, fill in the circle with the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

- O (0) I do not feel sad.
- O (1) I feel sad much of the time.
- O (2) I am sad all the time.
- O (3) I am so sad or unhappy that I can't stand it.

2. Pessimism

- O (0) I am not discouraged about my future.
- O (1) I feel more discouraged about my future than I used to be
- O (2) I do not expect things to work out for me.
- O (3) I feel my future is hopeless and will only get worse.

3. Past Failure

- O (0) I do not feel like a failure.
- O (1) I have failed more than I should have.
- O (2) As I look back, I see a lot of failures.
- O (3) I feel I am a total failure as a person.

4. Loss of Pleasure

- O (0) I get as much pleasure as I ever did from the things I enjoy.
- O (1) I don't enjoy things as much as I used to.
- O (2) I get very little pleasure from the things I used to enjoy.
- O (3) I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

- O (0) I don't feel particularly guilty.
- O (1) I feel guilty over many things I have done or should have done.
- O (2) I feel quite guilty most of the time.
- O (3) I feel guilty all of the time.

6. Punishment Feelings

- O (0) I don't feel I am being punished.
- O (1) I feel I may be punished.
- O (2) I expect to be punished.
- O (3) I feel I am being punished.

7. Self-Dislike

- O (0) I feel the same about myself as ever.
- O (1) I have lost confidence in myself.
- O (2) I am disappointed in myself.
- O (3) I dislike myself.

8. Self-Criticalness

- O (0) I don't criticize or blame myself more than usual.
- O (1) I am more critical of myself than I used to be.
- O (2) I criticize myself for all of my faults.
- O (3) I blame myself for everything bad that happens.

34113

Subject ID

Assessment

Feelings in the Past Month

CLL II Study - BDI-II

9. Suicidal Thoughts or Wishes

- O (0) I don't have any thoughts of killing myself.
- O (1) I have thoughts of killing myself, but I would not carry them out.
- O (2) I would like to kill myself.
- O (3) I would kill myself if I had the chance.

10. Crying

- O (0) I don't cry anymore than I used to.
- O (1) I cry more than I used to.
- O (2) I cry over every little thing.
- O (3) I feel like crying, but I can't.

11. Agitation

- O (0) I am no more restless or wound up than usual.
- O (1) I feel more restless or wound up than usual.
- O (2) I am so restless or agitated that it's hard to stay still.
- O (3) I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

- O (0) I have not lost interest in other people or activities.
- O (1) I am less interested in other people or things than before.
- O (2) I have lost most of my interest in other people or things.
- O (3) It's hard to get interested in anything.

13. Indecisiveness

- O (0) I makes decisions about as well as ever.
- O (1) I find it more difficult to make decisions than than before.
- O (2) I have much greater difficulty in making decisions than I used to.
- O (3) I have trouble making any decisions.

14. Worthlessness

- O (0) I do not feel I am worthless.
- O (1) I don't consider myself as worthwhile and useful as I used to.
- O (2) I feel more worthless as compared to other people.
- O (3) I feel utterly worthless.

15. Loss of Energy

- O (0) I have as much energy as ever.
- O (1) I have less energy than I used to have.
- O (2) I don't have enough energy to do very much.
- O (3) I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

- O (0) I have not experienced any change in my sleeping pattern.
- O (1a) I sleep somewhat more than usual.
- O (1b) I sleep somewhat less than usual.
- O (2a) I sleep a lot more than usual.
- O (2b) I sleep a lot less than usual.
- O (3a) I sleep most of the day.
- O (3b) I wake up 1-2 hours early and can't get back to sleep.

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Subject ID

Assessment

Feelings in the Past Month

CLL II Study - BDI-II

17. Irritability

- O (0) I am no more irritable than usual.
- O (1) I am more irritable than usual.
- O (2) I am much more irritable than usual.
- O (3) I am irritable all the time.

18. Changes in Appetite

- O (0) I have not experienced any change in my appetite.
- O (1a) My appetite is somewhat less than usual.
- O (1b) My appetite is somewhat greater than usual.
- O (2a) My appetite is much less than before.
- O (2b) My appetite is much greater than usual.
- O (3a) I have no appetite at all.
- O (3b) I crave food all the time.

19. Concentration Difficulty

- O (0) I can concentrate as well as ever.
- O (1) I can't concentrate as well as usual.
- O (2) It's hard to keep my mind on anything for very long.
- O (3) I find I can't concentrate on anything.

20. Tiredness or Fatigue

- O (0) I am no more tired or fatigued than usual.
- O (1) I get more tired or fatigued more easily than usual.
- O (2) I am too tired or fatigued to do a lot of things I used to do.
- O (3) I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

- O (0) I have not noticed any recent change in my interest in sex.
- O (1) I am less interested in sex than I used to be.
- O (2) I am much less interested in sex now.
- O (3) I have lost interest in sex completely.

22. Have you had **2 years or more** in your life when you felt depressed or sad most days, even if you felt okay sometimes?

- O (0) N/A
- O (1) No
- O (2) Yes

23. If you answered "yes" to item 22, have you felt depressed or sad much of the time **in the past year**?

- O (0) N/A
- O (1) No
- O (2) Yes

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