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# Predicting Medication Adherence Patterns During the Maintenance Phase of Treatment for Pediatric Leukemia and Lymphoma: A Model of Individual- and Family-Level Factors

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**Predicting Medication Adherence Patterns During the Maintenance Phase of Treatment for Pediatric Leukemia and Lymphoma: A Model of Individual- and Family-Level Factors**

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by
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Abstract

PREDICTING MEDICATION ADHERENCE PATTERNS DURING THE MAINTENANCE PHASE OF TREATMENT FOR PEDIATRIC LEUKEMIA AND LYMPHOMA: A MODEL OF INDIVIDUAL- AND FAMILY-LEVEL FACTORS

By Stephanie Romo, M.S.

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Adherence during the maintenance phase of pediatric cancer treatment is critical to prevent relapse and ensure long-term, event-free survival. Yet, little research has been done to examine individual- and family-level factors that may relate to adherence during the maintenance phase of treatment, particularly among Latinx patients. This is surprising given findings demonstrating that children who miss more than 5% of their prescribed oral chemotherapy medicine, most commonly 6-mercaptopurine (6MP), are 2.5-2.7 times more likely to relapse than children who take 95% or more of their prescribed 6MP. Pediatric cancer patients face unique adherence challenges given the importance of family involvement in children's care. As such, it is important to consider both individual- and family-level factors when examining adherence. **Objective.** Conducted a secondary data analysis to investigate individual- and family-level

factors that may predict 6MP medication adherence patterns, in a multisite cohort of pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) or lymphoblastic leukemia (LBL), in a sample that is 34% Latinx. **Methods.** Participants included 139 patients ages 7-19 years diagnosed with ALL or LBL, across six centers. Medication adherence was measured daily for 15 months using electronic monitoring of 6MP. At baseline, 6 months, and 15 months, participants reported on individual- (e.g., child depressive symptoms, caregiver depressive symptoms, child/adolescent health beliefs) and family-level (e.g., caregiver-child communication, younger children within the home) factors that might predict adherence patterns. Medical history was evaluated via standardized medical chart reviews at baseline, 6 months, 15 months, which included information on prescribed daily 6MP dose and duration of cancer diagnosis. **Results.** Results demonstrated characteristic differences between the adherence groups (e.g., age, dose, health beliefs). Results further indicated that developmental age group was the strongest predictor of medication adherence, such that youth in the middle-late adolescence age group were significantly more likely to be in the nonadherent group than youth in the preadolescent or early-middle adolescence age groups. Dosage and health beliefs, specifically positive outcome expectancy, also significantly predicted adherence group membership. Preliminary exploratory analyses indicate that predictors of adherence may differ between Latinx and non-Latinx, white patients. These results must be interpreted cautiously as the current study focused on outcomes rather than processes and social stratification. Furthermore, exploratory analyses indicated that adherence and quality of life were not significantly related in the current study, in either direction. **Conclusions.** Older adolescents may be at increased risk for nonadherence, which is an area of major concern warranting future research in this area. Findings also indicate that fostering positive outcome expectancy among youth at the start of maintenance phase may serve to enhance

adherence during this phase of treatment. Future work examining adherence behaviors should continue to assess longitudinal individual, family, and medication-level factors.

# Introduction

## Childhood Cancer: Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

Advancements in treatment for pediatric cancer over the last five decades has resulted in significant improvements in survival. Overall survival rates for childhood cancer have increased from 58% in 1975 to over 85% in 2020 (Howlader et al., 2020; Jemal et al., 2013). While survival rates continue to vary by cancer type (Howlader et al., 2020), increases in overall survival rates are largely attributed to participation in clinical trials that investigate efficacy and side effects of multimodal cancer treatments (G. T. Armstrong et al., 2016; Brennan et al., 2010; Hudson et al., 2012). Despite these critical improvements in care, cancer remains the second-leading cause of death among youth (Heron, 2019). It is estimated that approximately 1,050 children and 550 adolescents will die from cancer in 2022 (American Cancer Society, 2022; Siegel et al., 2021).

Leukemias are the most common childhood cancers with the most common being acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). These cancers of the bone marrow and blood account for roughly 28% of all cancers diagnosed in childhood (American Cancer Society, 2019). Brain and spinal cord tumors are the second most common cancers in children, making up about 26% of childhood cancers (American Cancer Society, 2019). Hodgkin and Non-Hodgkin Lymphomas, cancers of the lymphatic system, are the third most common cancers diagnosed in children (National Cancer Institute, 2020). Lymphoblastic lymphoma (LBL), which is treated similarly to ALL, primarily affects children and accounts for 25% to 30% of all non-Hodgkin lymphomas in children (American Cancer Society, 2016).

While there is ongoing debate concerning whether LBL and ALL are two presentations of the same disease or two distinct diseases, they are commonly considered to be part of a spectrum of malignant lymphoproliferative disorders (Kelly et al., 2018; Reddy & Perkins,

2004). The cancer cells of both ALL and LBL are very young lymphocytes called lymphoblasts (Kelly et al., 2018). Patients with ALL present with at least 25% of their bone marrow made up of lymphoblasts, whereas patients with LBL present with a mass and less than 25% bone marrow lymphoblasts (American Cancer Society, 2016). Similarities in morphology, genetics, and immunophenotypes have resulted in patients with ALL and LBL being treated on similar treatment protocols (Cortelazzo et al., 2017; Reiter et al., 2000; Weiss et al., 1986).

While specific treatment protocols for both ALL and LBL can differ based on staging results (e.g., cancer phenotype, genotype, and risk), treatment protocols consistently involve an intensive phase of cancer treatment followed by a maintenance phase (Asselin et al., 2011; Lau et al., 1998; Pui & Evans, 2006; Reiter et al., 2000). The duration of the intensive phase can range from several months to one year depending on diagnosis, sex, age, response to treatment, and clinical severity (Cortelazzo et al., 2017; Lau et al., 1998; Pai et al., 2008). This intensive phase of cancer treatment typically involves extensive inpatient admissions; four or five medications administered in clinic and during hospitalizations, most of which are administered intravenously; and in some cases, at-home nursing care visits following hospital discharge (Colby-Graham & Chordas, 2003; Pui & Evans, 2006).

The maintenance phase, also referred to as continuation treatment, begins once a patient's ALL or LBL is in remission. The primary goals of the maintenance phase of chemotherapy are to eliminate any residual cancer and prevent disease relapse. The maintenance phase of treatment can last for 2-3 years and involves multiple medications given on an outpatient basis (Cortelazzo et al., 2017; Lau et al., 1998; Pui & Evans, 2006). Maintenance therapy is considered vital for long-term, relapse-free survival for pediatric patients diagnosed with ALL and LBL (Bhatia et al., 2012, 2014, 2015; Kennard et al., 2004; Pritchard et al., 2006).

The maintenance phase necessitates that patients adhere to a long and complex course of treatment (Butow et al., 2010; Kazak et al., 2010; Malbasa et al., 2007; Wu et al., 2018). Throughout maintenance, patients are prescribed several oral medications, some of which are required daily (e.g., oral chemotherapy), weekly (e.g., methotrexate), and monthly (e.g., 5 day course of corticosteroids; Davies & Lilleyman, 1995; Landier, 2011). In addition to these scheduled oral medications, patients take other medications as needed (e.g., pain medication, vitamin D), attend monthly medical follow-ups, and receive monthly injections of vincristine (Kondryn et al., 2011; Malbasa et al., 2007; Pai et al., 2008). A daily dose of oral chemotherapy medication, most commonly 6-mercaptopurine (6MP), is a key element of ALL and LBL treatments often ranging between 550 to 1200 doses over the course of maintenance treatment. 6MP is most commonly administered in pill form and is only available in 50mg tablets. This complex and multifaceted treatment can be very challenging for children, adolescents, and their families (Kondryn et al., 2011; Malbasa et al., 2007; Pai et al., 2008; Pritchard et al., 2006; Wu et al., 2018), ultimately affecting their adherence to treatment recommendations.

**Scope, Prevalence, and Impact of Medical Nonadherence**

The World Health Organization (WHO), defines adherence as the ability for a patient to take medication as prescribed by a health care provider (WHO, 2003a). When describing patient health behaviors, the term "adherence" is preferred to the term "compliance" (Haynes, 1979; Verma & Rohan, 2020), as the term adherence reduces the implicit reference to the authority or power healthcare providers hold over a patient's health behaviors (i.e., "you must do what I say") and acknowledges the important role of the patient in their own treatment (i.e.., "we both have a part to play in your treatment journey"; Kyngäs, Duffy, et al., 2000; Santer et al., 2014; Verma & Rohan, 2020). Adherence can be differentiated from "concordance," which emphasizes a shared decision among equal partners in a therapeutic alliance (Drotar & Rohan, 2014; Horne, 2006).

However, some recommendations, such as medication treatment regimens, cannot be shared decisions given that patients must follow prescribed treatment regimens reasonably closely to what is recommended to achieve the full benefits of a medication regimen (Osterberg & Blaschke, 2005).

Nonadherence to medical treatments is defined as not completing a treatment regimen as prescribed or recommended by a health care provider (Cortina et al., 2013; Osterberg & Blaschke, 2005; Rapoff, 2010; Rohan et al., 2017). Across pediatric chronic illnesses, nonadherence to prescribed treatment regimens is a significant concern, with nonadherence prevalence rates estimated at 50% or greater among children (Rapoff, 2010; World Health Organization, 2003b) and ranging between 21-63% among adolescents (Butow et al., 2010; Hommel et al., 2009; Kondryn et al., 2011; McGrady & Hommel, 2013). Consequences of nonadherence across chronic illness populations include: increased symptoms, disease relapse, drug resistance, worse treatment outcomes, increased morbidity and mortality, lower health related quality of life, and increased health care utilization (Bae et al., 2011; Cortina et al., 2013; Drotar & Rohan, 2014; Kennard et al., 2004; McGrady & Hommel, 2013; Osterberg & Blaschke, 2005; Pai & Drotar, 2010; Rapoff, 2010; Rohan et al., 2010; Verma & Rohan, 2020; World Health Organization, 2003b). Past work has highlighted that as pill burden (i.e., number of pills taken daily) increases, adherence typically decreases (Schlatter et al., 2016; Silverstein et al., 2014). Furthermore, current literature indicates that adherence rates are typically higher among patients prescribed medication for short-term, acute conditions, and lower for patients whose chronic conditions require long term medication management (Kondryn et al., 2011).

The importance of consistent treatment adherence in the health outcomes of patients with ALL and LBL is underscored in the literature. Nonadherence to cancer treatment is known to impact morbidity and mortality in pediatric patients (Bhatia et al., 2012, 2014; Lau et al., 1998).

Treatment nonadherence may be related to clinical outcomes, such as worse disease prognosis, and increased risk of adverse side effects, disease relapse, late effects of chemotherapy treatment, and mortality (Bhatia et al., 2012, 2014, 2015; Davies & Lilleyman, 1995). Furthermore, research indicates that treatment nonadherence may impact clinical biomarkers (e.g., neutrophil counts and white blood cell counts), which provide information related to a child's ability to fight infections and influence chemotherapy dosing decisions (Bhatia et al., 2015; Haddy et al., 1999; Lau et al., 1998; Lennard et al., 1993; Rivera et al., 2003; Schmiegelow et al., 2014). Dosing titration decisions are largely based on a child's absolute neutrophil count. Given that appropriate dosing of 6MP is critical to achieve optimal medical outcomes and survival, nonadherence to 6MP is cause for major concern (Malbasa et al., 2007).

The current literature elucidates that nonadherence to prescription medication, including 6MP, during the maintenance phase of treatment is common in children and adolescents diagnosed with cancer (Bhatia et al., 2014, 2015; Davies & Lilleyman, 1995; Kondryn et al., 2011; Lau et al., 1998; Psihogios et al., 2021; Rohan, Drotar, et al., 2015). Forty-four percent of youth enrolled in a large Children's Oncology Group (COG) study were identified as nonadherent over the six month study period (Bhatia et al., 2012). Moreover, this research group reported that 47% of the relapses observed in the COG cohort were attributable to nonadherence (Bhatia et al., 2012). Additionally, this research group established 95% adherence to 6MP during maintenance phase as a critical cut-off level associated with a decreased risk of relapse (Bhatia et al., 2012, 2015). Specifically, youth who missed more than 5% of their prescribed oral chemotherapy doses were 2.5 to 2.7 times more likely to relapse than youth who were at least 95% adherent to 6MP (Bhatia et al., 2012, 2015). Given the significant impact of nonadherence to 6MP and other oral chemotherapies, the accurate identification of patients struggling with adherence is crucial to facilitate targeted interventions and support.

**Measurement of Adherence to 6-Mercaptopurine Medication in Pediatric ALL and LBL**

Nonadherence can vary from the occasional missed dose to complete refusal (Bhatia et al., 2014; Rapoff, 2010; Rohan & Winter, 2021; Verma & Rohan, 2020). Accordingly, it is critical to utilize methods that capture granular levels of adherence behaviors. Systematic and reliable objective measurement of treatment adherence in pediatric chronic illness is necessary, as findings demonstrate that medical providers are often unable to accurately detect nonadherence using subjective methods (Morisky et al., 1986; Pruette et al., 2019; Wagner et al., 2001). Patient and caregiver reports also routinely overestimate adherence levels (Kenna et al., 2005; Landier et al., 2017; Lau et al., 1998; Wagner et al., 2001) and often do not align with objective monitoring data (Pruette et al., 2019). Kenna and colleagues (2005) suggest that adherence measures be considered in two categories: 1) direct measures, such as observation of medication ingestion or biological assays; and 2) indirect measures, such as patient-/caregiver-report (subjective), prescription monitoring (objective), pill count (objective), or electronic monitoring (objective). A wide range of adherence measures are accessible; however, each is subject to their own strengths and limitations with biological assays and electronic monitoring often being considered the gold standard for assessing adherence (Drotar & Rohan, 2014; Kondryn et al., 2011; Wu et al., 2013).

Many studies investigating adherence to medication regimens in pediatric ALL and LBL, have relied on physician-, patient-, or caregiver- reported adherence (Kondryn et al., 2011; McGrady & Pai, 2019). However, as noted above, person-reported adherence is often inaccurate and, consequently, not ideal for accurately capturing and targeting nonadherence. Similarly, measuring adherence via pill counts often leads to overestimations of adherence rates and lacks objective data such as date and time medication was administered (Kenna et al., 2005). Conversely, while electronic monitoring data provides information regarding the date and time the medication cap was opened (Kenna et al., 2005; Vrijens et al., 2005), it does not directly

assess ingestion. Moreover, research has found that patients might occasionally open the bottle or remove medication from the bottle, but not actually ingest the medication (Cain et al., 2020; Kenna et al., 2005; Lau et al., 1998; Psihogios et al., 2021). Direct measures such as biological assays often provide the most reliable information about medication adherence; however, these measures are costly, sometimes impractical, and do not provide information about the underlying causes or patterns of nonadherence (Butow et al., 2010; Cain et al., 2020). Thus, Kenna and colleagues (2005) suggest utilizing multiple methods of adherence measures when possible. Using a combination of direct and indirect objective adherence measures can also provide validation of clinical findings, offering more insight into what specific areas patients are struggling with most, which can better inform adherence promotion interventions (Cortina et al., 2013; Rohan et al., 2017; Rohan & Winter, 2021).

**Limitations in Previous Research**

While past work investigating medication adherence in the maintenance phase has been conducted, they are not without limitations. First, the generalizability of previous work is limited due to small sample sizes (e.g., $N$ = 18 to 68), collection of data from a single site (Buchanan et al., 2014; Davies & Lilleyman, 1995; McGrady & Pai, 2019; Partridge et al., 2002; Pritchard et al., 2006; Ruddy et al., 2009), and lack of representation of minoritized ethnic groups. Particularly underrepresented are Latinx patients. To our knowledge, only three studies examining adherence during the maintenance phase have recruited a 10% or greater Latinx sample and reported on findings specific to Latinx children (Bhatia et al., 2012; Landier et al., 2017; Rohan et al., 2015). This is surprising given that the Latinx population accounted for 16% of the U.S. population in 2010 and 19% in 2020 (N. Jones et al., 2021) and that Latinx pediatric cancer patients are known to have higher rates of disease relapse and mortality (Bhatia et al., 2002; Kadan-Lottick et al., 2003; Milam et al., 2015). Second, previous research has typically relied on provider- or self-

reported adherence measures, which are known to overestimate adherence levels, and few have used combination of direct and indirect objective adherence measures (Kondryn et al., 2011; Lau et al., 1998; McGrady & Pai, 2019). Third, much of the research investigating medication adherence among pediatric patients with ALL and LBL has been cross-sectional or time-limited (e.g., a few weeks to a month), which restricts our understanding of adherence over the course of the maintenance phase (Hawwa et al., 2009; Kondryn et al., 2011; Lau et al., 1998; McGrady & Pai, 2019).

To date, eight studies have enrolled relatively large samples ($N$ = 139 to 900) across multiple sites (Bhatia et al., 2012, 2014, 2015; Kato et al., 2008; Lennard et al., 1995; Rohan et al., 2017; Rohan, Drotar, et al., 2015; Wu et al., 2018). The duration of these larger studies ranged from 1 month to 2.5 years. Adherence rates were established via medication refill analysis (Wu et al., 2018), electronic monitoring (Bhatia et al., 2012, 2014, 2015; Rohan, Drotar, et al., 2015), biological assays (Lennard et al., 1995; Traore et al., 2006), a combination of self-reported adherence data and metabolite levels (Hawwa et al., 2009) and a combination of electronic monitoring and assay data (Kato et al., 2008; Rohan et al., 2017). Among the studies utilizing these data to evaluate adherence over time, the majority identified patients who were adherent or not adherent using dichotomous metrics and few explored subgroups of children with different trajectories of adherence over time.

To our knowledge, only one study has utilized latent group-based trajectory modeling to identify patterns of nonadherence to 6MP during the maintenance phase (Rohan, Drotar, et al., 2015). Rohan et al. (2015) examined linear trajectories of adherence across one-month and identified three mutually exclusive adherence patterns: (1) optimal adherence (e.g., nearly 100% adherence across time), (2) deteriorating/moderate adherence (e.g., decrease from 100% to 60% adherence over time), and (3) chronic nonadherence (e.g., approximately 40% adherence over

time). Furthermore, within these larger, longitudinal studies the relationship between medication adherence and individual- and family-level factors were not explored. For instance, it is possible that different individual- and family-level factors may predict medication adherence. Understanding patterns of adherence and how individual- and family-level factors influence adherence over time is essential to the development of innovative patient- and family-centered interventions to minimize adherence barriers, identify much-needed resources for continued success, and to maximize facilitators to adherence, which will ultimately improve outcomes.

## Factors Associated with Adherence in the Maintenance Phase of Pediatric Cancer Treatment

Adherence to 6MP in the maintenance phase is multifaceted and influenced by several factors. As noted above, much of the work examining adherence in the maintenance phase of pediatric cancer treatment is limited. Furthermore, systematic reviews exploring factors related to adherence have demonstrated that many of the studies examining potential factors were conducted roughly two decades ago and few attempted to determine underlying reasons for nonadherence (Butow et al., 2010; Festa et al., 1992; Gupta & Bhatia, 2017; Lancaster et al., 1997; Lansky et al., 1983; McGrady & Pai, 2019; Partridge et al., 2002; Ruddy et al., 2009; Tebbi et al., 1986). Notwithstanding, the current literature elucidates that adherence patterns for pediatric and adolescent patients with cancer may be related to several distinct factors.

**Treatment-Level Factors.** Adherence patterns may be associated with treatment-related factors such as disease or treatment duration, insurance, timing of medication administration, and medication dosage (which may serve as a proxy measure of pill burden if the patient is required to take more than one pill in a single administration or medication multiple times a day). Indeed, lower rates of adherence have been associated with treatment related factors such as: when medication is taken (e.g., decreased adherence over weekend compared to weekday; Psihogios et

al., 2021), reliance on Medicaid or the Children's Health Insurance Program (Wu et al., 2018), higher 6MP dosage (Bhatia et al., 2015), and treatment duration (e.g., adherence patterns decrease over time or the longer you have to take a daily oral medication; Bhatia et al., 2012, 2014; Rohan et al., 2015). Adherence is also known to be associated with non-treatment related factors, including individual- and family-level factors.

**Individual-Level Factors**. Adherence can also be related to several individual-level factors. For example, lower adherence rates have been associated with factors such as lower motivation/decreased mood (Psihogios et al., 2021). There is substantial evidence that patients diagnosed with oncology disorders often report increased psychological distress including higher levels of anxiety and depression, decreased physical activity, increased fatigue, and decreased quality of life (QoL) across their illness trajectories (Armenian et al., 2013; Kahalley et al., 2013; Kazak & Noll, 2015; Paltin et al., 2018). In a study investigating the psychological needs of adolescent and young adult (AYA) cancer survivors, 82% of cancer survivors expressed having at least one concern related to behavioral, cognitive, and emotional domains across their illness trajectories, from diagnosis to survivorship (Paltin et al., 2018). There are a number of factors associated with depressive symptoms that might impact maintenance phase adherence, including feelings of hopelessness (e.g., feeling that treatments are not worthwhile), social withdrawal and/or isolation (e.g., absence of necessary emotional support and assistance from others), and cognitive impairments (e.g., forgetting, errors in self-management; DiMatteo et al., 2000; Drotar & Rohan, 2014; Wu et al., 2010). While the relationship between patient depression and adherence have not been explored in the maintenance phase of pediatric cancer treatment, past work with children with cystic fibrosis demonstrated that increased child depressive symptoms predicted significantly lower rates of adherence to airway clearance (Smith et al., 2010). Similarly, past work with adolescents with inflammatory bowel disease found that youth with

higher anxiety/depressive symptoms reported lower adherence (Gray et al., 2012). As such, exploring youth-reported depressive symptoms as a possible factor related to adherence during maintenance treatment is warranted.

Studies focused on caregivers' psychosocial functioning during cancer treatment have demonstrated similar increases in anxiety, stress, and depression over the course of treatment (Katz et al., 2018; Rosenberg et al., 2014). Although the relationship between caregiver depression and adherence in the maintenance phase has not been explored, past work examining adherence in children with asthma found that higher maternal depressive symptoms were related with forgetting to give their child their medication (Bartlett et al., 2004), less confidence in managing their child's asthma (Bartlett et al., 2004), and decreased adherence (Bartlett et al., 2004; Margolis et al., 2021, 2022). Given caregivers' important involvement in pediatric cancer treatment, including administering their child's medication, it is possible that caregiver depressive symptoms also significantly relate to adherence to 6MP during the maintenance phase.

While patient and caregiver QoL have also been extensively examined over the course of cancer treatment (Armenian et al., 2013; Bakula et al., 2020; DeWalt et al., 2015; Hullmann et al., 2010; Kazak & Barakat, 1997; Klassen et al., 2011; Langeveld et al., 2002; McDougall & Tsonis, 2009; Mullins et al., 2016), our understanding of the relationship between QoL and medication adherence remains limited. Past research examining the relationship between adherence and QoL within samples of children with chronic conditions (e.g., irritable bowel disease, liver transplant, sickle cell disease, asthma), demonstrates a potentially bidirectional relationship. For example, across pediatric chronic conditions, nonadherence may have an impact on QoL as a result of the need to miss school or social activities because of hospitalizations and medical appointments (Rapoff, 2010). Specifically, among pediatric liver transplant recipients, adolescents with lower adherence reported more limitations in social and school activities related to physical, emotional,

and behavioral problems (Fredericks et al., 2008). Additionally, in a sample of pediatric patients with Crohn's, nonadherence to their immunosuppressant medication (e.g., 6MP, 1-2 pills a day), as measured by biological assay, was related to decreased patient-reported physical health QoL (Hommel et al., 2009).

Previous work has also demonstrated that adherence can negatively impact QoL. For example, pediatric patients with Crohn's who reported greater self-reported adherence to their inflammation medication (e.g., 5-ASA, 12-18 pills a day) reported lower overall psychological QoL (Hommel et al., 2009). This is consistent with past work highlighting inverse relationships between routine burden and QoL among pediatric patients with asthma (Fiese et al., 2005) and adherence and QoL among pediatric patients with sickle cell disease (Barakat et al., 2005). Similar relationships may exist between 6MP adherence and QoL among pediatric cancer patients in the maintenance phase of treatment. For example, nausea is a known side effect of 6MP and patients receiving cancer treatment have reported greater nausea than patients off treatment on cancer-specific HRQoL measures (Varni et al., 2002). Thus, it is possible that greater adherence could result in increased nausea and, consequently, greater nausea may result in nonadherence. While the relationship between adherence and QoL has not been explored during the maintenance phase of cancer treatment, it is possible that a bidirectional relationship may also exist among pediatric patients with cancer.

Further, perceived health beliefs (e.g., lower perception of illness severity) can also affect adherence rates (Jamison et al., 1986). A systematic review of qualitative studies exploring caregivers' views of adherence in chronic pediatric conditions, not including cancer, indicated that a main factor associated with adherence are beliefs about the condition or treatment (Santer et al., 2014). Specifically, patients and families reported weighing the perceived effectiveness or necessity of medication versus the fears of side effects and other concerns (Santer et al., 2014).

While past work examining adherence in the maintenance phase of pediatric cancer has not examined how beliefs about medication relate to adherence, it is possible that these beliefs influence children's health behaviors. Indeed, a focus group study exploring adherence barriers among adolescents in the maintenance phase indicated that favorable blood counts after periods of intermittent nonadherence (e.g., missing medication for a week) made them view the medication regimen as less necessary as there were no immediate negative consequences for their health behaviors (Malbasa et al., 2007). As such, patient's health beliefs related to the maintenance phase of treatment, particularly the positive outcomes they expect from adhering or not adhering to treatment, and the negative effects they fear will occur from following their treatment regimen, may impact their adherence over time.

It is well documented that there is individual variability in health behaviors across the illness trajectory, especially within adolescent oncology populations. In fact, lower adherence over the course of treatment is often related to transitioning into adolescence (Bhatia et al., 2012; Jamison et al., 1986; Mancini et al., 2012; Partridge et al., 2002; Reed-Knight et al., 2014). Furthermore, adolescent oncology patients often report increased neurocognitive deficits, including deficits in executive functioning, memory, concentration, and attention, which may ultimately lead to worse adherence patterns (Evan & Zeltzer, 2006; Gutiérrez-Colina et al., 2016; Kazak & Noll, 2015). Adolescent patients with cancer also have unique developmental challenges compared to their younger peers (Landier, 2011). Both pediatric and adolescent patients report increased psychological distress, adjustment difficulties, and decreased quality of life; however, adolescent patients often report additional difficulties specific to this challenging developmental period, including: a threatened sense of safety and reduced security, feelings of loss of control, body image concerns, decreased self-esteem and modified sense of self, difficulties with interpersonal relationships, disruptions in daily life (e.g., academics, employment), increased

caregiver-adolescent conflict, and a threatened sense of independence (Evan & Zeltzer, 2006; Sisk et al., 2019; C. E. Wakefield et al., 2010). The developmental difficulties of transitioning from middle to late adolescence are often amplified for adolescents with chronic illnesses. In fact, across pediatric chronic illness populations, many emerging adolescents and their parents report difficulties with balancing parental monitoring and support while avoiding unnecessary reminders that seem like trivial "nagging" and ultimately result in adolescent rebellion (Mulvaney et al., 2008; Naimi et al., 2009; Rohan & Winter, 2021; Taddeo et al., 2008). Moreover, parents often report ongoing difficulties between supporting adolescent autonomy while minimizing risk for prematurely transferring responsibility for self-management completely to the adolescent (Peterson-Sweeney et al., 2003; Reed-Knight et al., 2014). Additionally, past work has demonstrated that children's perceptions of caregiver involvement evolve across developmental phases (Taylor et al., 2010). As such, developmental phase during the maintenance phase of treatment is an important variable to consider as a potential predictor of adherence behaviors.

Particularly among adolescents, patients found to be nonadherent to their cancer treatment regimen reported higher levels of depression, lower self-esteem, higher levels of caregiver-child relationship discord (e.g., poor communication, increased conflict), and incongruent reports of home environment/family functioning patterns between adolescents and their parents (Kennard et al., 2004). Simultaneously, research demonstrates that adherence rates can be positively impacted by targeted interventions, such as daily reminders (Psihogios et al., 2021) and playing video games focused on managing cancer treatment and the common issues associated with managing such a complex regimen (Kato et al., 2008). As such, identifying and understanding the individual- and family-level factors related to adherence may better inform future intervention development geared at addressing these modifiable factors related to adherence.

**Family-Level Factors.** When considering family-level factors in children's adherence, it is clear that pediatric treatment adherence is impacted by unique challenges due to the critical importance of family involvement in care (Drotar & Rohan, 2014; Riekert & Drotar, 2000; Rohan & Winter, 2021). Children depend on their caregivers in numerous ways, as caregivers are often responsible for acquiring, dispensing, and monitoring medications. Typically, as children age and demonstrate increased responsibility, autonomy, and independence, treatment responsibilities become shared between adolescents and their caregivers. Past work has highlighted that behavioral challenges related to adherence during cancer treatment can evolve as children age (Landier, 2011). For example, babies may have difficulties swallowing medication, young children may dislike the taste of oral medication, and adolescents may begin to refuse medications. As children begin to transition into adolescence, their desire for autonomy may increase, while their ability to understand long-term consequences are still developing (Landier, 2011).

Prior research has hypothesized that caregiver-child relationship dynamics, including a lack of communication and increased conflict, between caregivers and adolescents regarding who is responsible for monitoring or administering medication may be related to lower adherence rates in adolescence (Tebbi, 1993). Indeed, past work exploring adherence to medication among adolescents with chronic illnesses, including pediatric cancer, found that positive family relationships and open communication supported adherence (Jamison et al., 1986; Kennard et al., 2004; Kyngäs, Kroll, et al., 2000; Rohan & Winter, 2021). Similarly, families with higher conflict and/or poorer communication styles, had higher rates of nonadherence (DiMatteo, 2004). Accordingly, considering youth's family context in the form of caregiver-child communication and conflict dynamics is critical when examining factors that may relate to adherence during the maintenance phase of treatment.

Another important factor to consider when assessing youth's family context is the makeup of their home, as it often shapes family daily life. Past research examining treatment nonadherence in youth with chronic medical conditions that require daily medication (e.g., asthma, diabetes, HIV) found that parents often report feeling as though adherence behaviors need to be considered in the context of balancing the everyday needs of their child with a chronic illness within the daily needs of the family (Rohan & Winter, 2021; Santer et al., 2014; Verma & Rohan, 2020). This balancing often involves considering the needs of other children and members in the home. It has been posited that the individualized needs of siblings can complicate family routines around medication management in homes where a child has a chronic illness (Fiese et al., 2005). Furthermore, past reports indicate that caregivers note the stress of getting their children to school in the morning as a barrier to antiretroviral medication adherence in young children infected with HIV (K. J. Roberts, 2005). It is possible that the presence of children or siblings in the home who are younger than the patient, and potentially need more caregiver attention and support, causes competing demands for caregivers trying to maintain family routines around medication management (Fiese et al., 2005). While this past work was not specific to children in treatment for pediatric cancer, it is possible that caregivers may weigh similar factors when managing daily medications regimens in the maintenance phase. Indeed, prior work found that the number of siblings in the home was negatively correlated with cancer treatment adherence (Tebbi et al., 1986). Although factors such as caregiver-child communication and number of younger siblings/children in the home have not been explored during maintenance phase of cancer treatment, it is possible that these family-level factors may impact youths' adherence.

Significant economic, ethnic, and racial disparities in clinical outcomes for pediatric patients diagnosed with cancer are well documented (Bhatia, 2011; Bhatia et al., 2012; Buchanan

et al., 2014; Pritchard et al., 2006). Having a child diagnosed with pediatric cancer could have negative impacts on the entire family system, including: an impact on parent/caregiver employment, finances, and sources of emotional and social support (Kazak et al., 2015; Wiener et al., 2015). Additionally, minoritized children may have an increased risk for medication toxicities, which may contribute to increased family stress and a higher risk of nonadherence (Bhatia, 2011; Bhatia et al., 2012). In fact, longitudinal data from a large cohort of children with leukemia ($N$ = 575) demonstrated those from high poverty areas were more likely to experience inferior overall survival rates compared to patients from low poverty areas (Bona, 2018). Furthermore, some past work has indicated varying levels of adherence among minoritized and non-minoritized youth with cancer (i.e., Latinx, Black, and Asian; Bhatia et al., 2012, 2014), while other work has found no ethnic group differences (Rohan, Drotar, et al., 2015). Moreover, while exploring the relationship between demographic factors (e.g., family structure, household income, parental education) and adherence rates within the COG cohort, Bhatia and colleagues (2012, 2014) demonstrated that these associations can vary across racial/ethnic groups. For example, while parental education was significantly related to adherence among Black (maternal education) and non-Latinx white (paternal education) children, it was not related to adherence among Asian (Bhatia et al., 2014) or Latinx children (Bhatia et al., 2012). Moreover, while Black and non-Latinx white children had higher adherence in single-parent/single-child households than in "nuclear family" households (Bhatia et al., 2014), Latinx children in single-parent households had lower adherence rates (Bhatia et al., 2012). Lastly, while household income impacted Asian patients' adherence, household income was not related to adherence among Black, Latinx, or non-Latinx white children (Bhatia et al., 2012, 2014). Of note, Bhatia and colleagues did not consider the intersection between race and ethnicity (Bhatia et al., 2014); thus, it is unclear if any of the Black or Asian children in their sample were also Latinx. Furthermore,

while this work indicates that demographic factors may differentially affect adherence in these diverse groups, these demographic level factors do not shed light on the mechanisms or underlying causes of these relationships. Nevertheless, these results highlight the importance of improving our understanding of which factors influence adherence not just among the greater pediatric cancer population, but within racial and ethnic groups.

**The Importance of Including Latinx Pediatric Cancer Patients in Clinical Trials**

Simply comparing rates of adherence across racial and ethnic groups is not enough to understand the nuances of adherence and nonadherence in these unique groups. Despite guidelines calling for the inclusion of minoritized youth in clinical trials and cancer research (National Institutes of Health, 2001), the current literature on childhood cancer patients indicates that those from diverse racial and ethnic backgrounds are seldomly included (Aristizabal et al., 2015; Burke et al., 2007; Chen et al., 2014; Faulk et al., 2020; Ford et al., 2008; Samuel et al., 2020; Sateren et al., 2002; Underwood, 2000). Particularly underrepresented are Latinx childhood cancer patients (Carney et al., 2020; Munet-Vilaró, 2004; Samuel et al., 2020; Walsh & Ross, 2003). Although systematic reviews have reported on Latinx cancer patients' outcomes, this work has largely focused on adulthood breast cancer (Samuel et al., 2020). The lack of representation of Latinx childhood cancer patients has been attributed to exclusion based on language requirements, barriers to participation, and issues reporting racial/ethnic categories (Aristizabal et al., 2015; Giuliano et al., 2000; Gray et al., 2014; Walsh & Ross, 2003; Yancey et al., 2006).

While total cancer rates for Latinx children are lower than their non-Latinx white counterparts, incidents of ALL are approximately 20% higher among Latinx children (Miller et al., 2018). Additionally, Latinx children are known to have lower rates of leukemia survivorship (Bhatia et al., 2002; Kadan-Lottick et al., 2003; Miller et al., 2018) and may be less likely to

access survivorship clinic follow-up care (Isaac et al., 2020; Klosky et al., 2008; Milam et al., 2015). These incongruences have been closely associated with socioeconomic status, insurance status, and access to quality health care (Bhatia et al., 2002; Miller et al., 2018). Due to disparities in access to healthcare, Latinx children diagnosed with cancer are often underserved and understudied (Cain et al., 2020; Jones et al., 2010).

Available data regarding adherence among Latinx children in the maintenance phase of treatment is limited (Bhatia et al., 2012; Landier et al., 2017; Rohan, Drotar, et al., 2015). Among the two studies examining adherence rates over time, one study reported lower rates of adherence among Latinx children when compared to non-Latinx white children (Bhatia et al., 2012), while the second did not find racial/ethnic differences related to adherence (Rohan, Drotar, et al., 2015). Of note, Bhatia and colleagues (2012) found that Latinx children in the COG cohort were at a 2.6-fold increased risk of disease relapse compared to non-Latinx white children. While past work has posited that the increased rate of relapse among Latinx children may be due to lower rates of medical adherence and follow-up visit attendance (Pritchard et al., 2006; Solari, 2014), Bhatia and colleagues (2012) demonstrated that risk of relapse differed by level of adherence. Specifically, while risk of relapse was comparable between Latinx and non-Latinx white children at adherence levels less than 90%, Latinx patients continued to demonstrate higher risk of relapse at adherence rates exceeding 90% (Bhatia et al., 2012). Investigators hypothesized that even in the presence of adequate systemic exposure to 6MP, underlying genetic factors may influence relapse risk among Latinx children (Bhatia et al., 2012).

Given that Latinx children who are adherent to their medication regimen continue to be at an increased risk of relapse, promoting and maintaining adherence among Latinx children is critical to help reduce modifiable risk factors associated with worse health outcomes. The third

study that examined adherence during the maintenance phase of treatment and recruited a 37% Latinx sample focused on a comparison of self-report and electronic monitoring of 6MP intake in childhood ALL (Landier et al., 2017). Results indicated that Latinx caregivers overreported adherence rates when compared to non-Latinx white caregivers (Landier et al., 2017). While reasons for overreporting were not explored, these results indicate that objective measures of adherence may help to better capture adherence within this population. A better understanding of adherence among Latinx pediatric cancer patients is needed to inform care and strengthen intervention relevancy to patients and their families (Bava et al., 2017; Coard et al., 2007; Munet-Vilaró, 2004). As such, the current study is poised to make a significant contribution to the literature with regards to understanding health behaviors and outcomes of Latinx children diagnosed with cancer in the maintenance phase of cancer treatment.

**Rationale and Significance of the Current Study**

The primary focus of the current study was to identify individual- and family-level predictors of medication adherence patterns during the maintenance phase of treatment for pediatric ALL and LBL patients ages 7-19 years (N = 139). Adherence to 6MP medication is critically important for the survival and long-term success of pediatric ALL and LBL patients. 6MP is an oral medication that is administered daily and can be feasibly and reliably monitored with measures such as electronic monitors (e.g., MEMS: AARDEX Corporation, Palo Alto, CA) and pharmacological measures such as biological assays. Prior research with this same cohort of pediatric patients (*N* =139) demonstrated that electronic monitoring and pharmacological measures of 6MP both validly and reliably described treatment adherence patterns over the course of 15-months within this sample (Rohan et al., 2017). Additionally, this past work established that results of the electronic monitoring data were directly related to the results of a pharmacological measure of treatment adherence. Those with low metabolite levels of 6MP

also had much lower adherence rates based on electronic monitoring and those with metabolite profiles indicating optimal adherence also had much higher adherence results (Rohan et al., 2017). Thus, electronic monitoring data is a valid indicator of 6MP adherence patterns over time in this sample and served as the adherence metric in the current study.

Prospective studies of adherence have generally noted deterioration in treatment adherence over time (Bhatia et al., 2012; Lau et al., 1998; Pai et al., 2008; Pritchard et al., 2006), but little is known about patterns and changes in 6MP medication adherence over time. Additionally, the relationship between individual- and family-level factors that may relate to adherence during the maintenance phase of treatment for pediatric cancer have largely been unexplored. Furthermore, this cohort of pediatric patients was intentionally recruited from sites known to serve Latinx communities to better understand adherence within this population. As such, this study addressed several limitations of previous research by using objective adherence data to describe the relationship between medication adherence and individual- and family-level factors over 15 months, within a sample that is 34% Latinx.

Past work has demonstrated that adherence can be related to individual-level factors such as health beliefs (Malbasa et al., 2007; Santer et al., 2014), child and parent emotional functioning (Kennard et al., 2004; Lansky et al., 1983; Psihogios et al., 2021), and family-level factors such as caregiver-child communication and conflict (Kennard et al., 2004; Kyngäs, Kroll, et al., 2000; Rohan & Winter, 2021) and number siblings (Tebbi et al., 1986). The current study expanded our understanding of how these factors might predict adherence patterns in the maintenance phase of pediatric cancer.

Furthermore, past work exploring the relationship between quality of life and medication adherence is limited. Likewise, the directionality of the relationship between quality of life and medication adherence is not well understood (Pai & Drotar, 2010). Past work within pediatric

populations with chronic illnesses (Barakat et al., 2005; Fiese et al., 2005; Fredericks et al., 2008; Hommel et al., 2009) indicate a potentially bidirectional relationship. As such, the current study aims to examine a bidirectional model of adherence predicting quality of life and quality of life predicting adherence; to better understand the relationship between quality of life and medication adherence during the maintenance phase of pediatric cancer.

**Specific Aims, Research Questions, and Hypotheses**

The current study has three proposed aims. See *Table* 1 for a description of the aims, hypotheses, and proposed data analyses. Prior research in this cohort of pediatric patients with ALL and LBL, aged 7-19 years, demonstrated three mutually exclusive patterns of treatment adherence over time, both across one month (Rohan, Drotar, et al., 2015) and across 15-months (Rohan & Geaney, 2018) of observation (*Figure 1*): optimal adherence (e.g., nearly 100% adherence across time), moderate adherence (e.g., average of 60% adherence over time), and (3) chronic nonadherence (e.g., approximately 40% adherence over time). The current study aims to extend past work describing adherence patterns during the maintenance phase of treatment across the first month (Rohan, Drotar, et al., 2015) and across 15-months (Rohan & Geaney, 2018) of adherence monitoring by further describing and examining individual and family-level predictors of 6MP adherence trajectories across 15 months.

**Aim 1:** Aim 1 was to describe the characteristics of patients following different adherence patterns across 15 months (i.e., optimal adherence, moderate adherence, chronic nonadherence). We hypothesized that youth in the moderate adherence and chronic nonadherence groups would be older than youth in the optimal adherence group. We also hypothesized that 6MP dosage would be variable across the three groups, with youth in the optimal adherence group having the lowest 6MP dose (i.e., less pill burden), youth in the moderate adherence group having the second lowest dose, and youth in the chronic

nonadherence group having the highest dose (i.e., greatest pill burden). This was a variable of interest given that the number of daily 6MP pills increases as the dosage increases ultimately leading to increased pill burden.

Due to the small sample sizes of both the chronic nonadherence ($n$ = 17) and moderate adherence ($n$ = 36) subgroups relative to the optimal adherence subgroup ($n$ =88), the chronic nonadherence and moderate adherence groups were combined into a single subgroup, referred to as the "nonadherent group," for all analyses discussed in Aims 2-3. The optimal adherence group was referred to as the "adherent group."

**Aim 2a:** Aim 2a was to identify predictors of 6MP medication adherence patterns in a cohort of pediatric cancer patients. We hypothesized that higher levels of caregiver and patient depression, greater number of younger siblings/children in the home, and higher beliefs of negative outcomes from taking medication would predict membership in the nonadherent group. We further hypothesized that more frequent communication, greater intent to adhere to treatment, and higher beliefs of positive outcomes from taking medication would predict membership in the adherent group.

**Aim 2b (Exploratory Analyses):** Aim 2b was an exploratory analysis to examine whether predictors of 6MP medication adherence differed between ethnic groups (i.e., Latinx, non-Latinx, white), similar to past work (Bhatia et al., 2012, 2014). Given past work demonstrated differences in adherence patterns across several demographic, individual, and family-level factors, we hypothesized that predictors of adherence might differ between Latinx patients and non-Latinx, white patients. Moreover, given that past research with this cohort (Rohan, Drotar, et al., 2015) did not find adherence differences across ethnic groups at one month, we do not have specific directions for these relationships.

**Aim 3 (Exploratory Analyses):** Multivariate models were used to examine bidirectional relationships between quality of life and 6MP adherence in a cohort of pediatric cancer patients during the maintenance phase of treatment. We hypothesized that behavioral patterns of nonadherence would predict lower total quality of life and lower rates of nausea. A second model was examined to determine if total quality of life and nausea-specific quality of life predicted adherence subgroup membership. It was hypothesized that quality of life (total, nausea-specific) would predict adherence subgroup membership, such that, those with high rates of total quality of life would be less likely to belong to the nonadherent subgroup and that those with higher rates of nausea would likely belong to the adherent subgroup.

## Methods

### Study Design

This research study was a secondary analysis of data collected as part of two studies, separately funded by the National Cancer Institute (1R01CA119162 to Drotar; 1F31CA168307 to Rohan). This prospective, multisite randomized controlled trial investigated a family-centered problem-solving intervention to promote medication adherence among pediatric cancer patients who were in remission and completing the maintenance phase of treatment. Adherence, psychosocial, and medical data were collected as part of this 15-month longitudinal RCT. The current research study focused on identifying individual- and family-level factors that predicted adherence patterns using electronic monitoring technologies. The proposed study aims, and data analytic plan are separate from the prior research proposed in the original grant submissions and the subsequent published papers from that grant. The research strategy, aims, and data proposed here are unique to this dissertation research.

Per HIPAA guidelines at the respective study sites, families were first contacted by their medical provider via letter or in-person to gain permission for the study team to approach the

family about the study. If families did not opt out of being contacted, they were approached by study coordinators at each site to obtain parental permission and consent and assent from children and adolescents ages 11 years and older. Verbal assent was obtained from patients 10 years and younger. Of the 171 patients and families approached to participate, 18.7% ($n$ = 32) refused to participate for the following reasons: being too busy ($n$ = 12), not interested ($n$ = 19), or having no transportation (n = 1). Past comparisons of patients' and families who participated in the study with those who did not participate indicated negligible associations with respect to patients' age ($d$ = -0.003) and gender ($F$ = 0.09, $p$ = 0.22; Rohan, Drotar, et al., 2015). However, there was a moderate association in participation rates by ethnic group: non-Latinx, white patients' and families refused participation more often (9.4%) compared to Latinx (3.5%) and non-Latinx, racially minoritized (5.8%) patients' and families (V = 0.23; p = 0.01; Rohan et al., 2017).

**Participants**

Participants were 139 children and adolescents ages 7-19 years who were diagnosed with ALL or LBL and their primary caregivers. All patients were expected to complete at least one cycle (84 days) of maintenance treatment prior to completing baseline measures. Patients and their caregivers were followed at six medical centers across the United States. Ethnicity distributions were largely representative of each clinic's sample. The parent study included two sites that predominately served the Latinx community and who had multilingual research coordinators and interventionists (Children's Hospital Los Angeles, Children's Medical Center Dallas). As such, within the sample 75 (54.0%) identified as non-Latinx, white; 16 (11.5%) identified as non-Latinx, racially minoritized; and 48 (34.5%) identified as Latinx.

At baseline, the mean age of the sample was 12.29 years (SD = 3.44, range 7-19 years). Sixty-eight percent of patients identified as male, while 32% identified as female. This is

characteristic of this type of diagnosis, which is known to affect more males than females. Duration of cancer diagnosis at baseline ranged from 0.68 to 2.27 years. Demographic and medical characteristics of the baseline sample are provided in *Table 2a*. Study procedures were approved by each site's Institutional Review Board.

**Eligibility Criteria**

To be eligible for study participation, participants were required to be diagnosed with ALL or LBL in remission, prescribed a daily dosage of 6-mercaptopurine (6MP) oral medication, and finished with at least one cycle (84 days) of the maintenance phase of therapy for ALL and LBL. Patients were excluded from recruitment efforts if they were diagnosed with a comorbid chronic condition requiring burdensome treatments (e.g., cystic fibrosis) or diagnosed with an intellectual disability or psychiatric condition making it difficult to complete study procedures. At time of study recruitment, additional eligibility criteria were reviewed with patients and families. Participants were excluded from study participation ($n$ = 7) if they were: involved in foster care or did not have a primary caregiver available to participate ($n$ = 2) or had known plans to relocate to another area requiring transfer of all medical care prior to study completion ($n$ = 5).

**Attrition Rates**

Past work examining attrition rates of the current sample (Rohan et al., 2017) indicated 12 participants (8.6%) dropped out of the study due to: disease relapse ($n$ = 9, 75%), completing maintenance therapy prior to study completion ($n$ = 1, 8.3%), and relocation/transfer of care to a new hospital ($n$ = 2, 16.7%). Of these families, 8.3% ($n$ = 1) completed baseline measures, 33.3% ($n$ = 4) completed 3 months measures, 25% ($n$ = 3) completed 6 months measures, 25% ($n$ = 3) completed 9 months measures, and 8.3% ($n$ = 1) completed 12 months measures. Those who dropped out of the study did not significantly differ from those who remained in the study with

respect to patients' cumulative behavioral adherence rates, age, and gender ($p > 0.05$). However, Latinx patients ($n = 8$) dropped out more frequently than non-Latinx, white ($n = 3$) and non-Latinx, racially minoritized ($n = 1$) patients ($V = 0.22$; $p = 0.04$).

**Family-Centered Problem-Solving Intervention**

Following the baseline study visit, youth and their primary caregivers were randomized in equal numbers to one of two groups using a stratified random permuted blocks scheme design: Family Problem Solving Training Intervention (FPST) (n = 69) or Current Psychosocial Care (CPC) (n = 70; Ko et al., 2021). The primary aim of the RCT involved testing the efficacy of an FPST intervention that addressed barriers to treatment adherence, including enhancing adolescent and family problem-solving strategies, facilitating caregiver-adolescent communication and collaboration, and using behavioral reinforcement to enhance problem-solving skills. The FPST intervention model was a family-based approach designed to address specific barriers to medication adherence that were commonly experienced by youth with cancer and their families. The FPST included five in-person visits and two phone visits that were designed to enhance the durability of intervention effects. The essential features of the intervention model involved the promotion of caregiver-adolescent problem-solving and team work in developing solutions to specific barriers to medication adherence, which were identified during the intervention sessions; improving youth-caregiver communication around cancer treatment and promoting development of collaborative strategies to improve medication adherence; promoting parental support and monitoring of medication adherence; and utilizing behavioral strategies to reinforce adherence to treatment, including engagement and enhancement of motivation and problem solving methods (Ko et al., 2021; Nezu et al., 1989).

**Measures**

**Linguistic Translation Procedures.** Twenty-nine parents and six teens completed measures in Spanish. Existing, validated Spanish-language measures were utilized when available. Measures not available in Spanish were translated for the current study. Materials were translated using a back-translation and forward-translation approach to maintain construct and conceptual equivalence (Knight et al., 2009; Sireci et al., 2006). Consistent with past studies involving Latinx pediatric cancer patients and their families (Meeske et al., 2004; Sahler et al., 2005; Varni et al., 2002), conceptual equivalence (e.g., consistent construct meaning across languages) was evaluated (MAPI Research Institute, 2019). Principal investigators at the Los Angeles and Dallas sites worked closely to ensure that translated materials were applicable to the families at each site. Similar to a prior multisite problem-solving intervention program in pediatric oncology that used an index dialect (Sahler et al., 2005), the Mexican dialect was utilized across measures, as the majority of Latinx patients and families in Los Angeles and Dallas were of Mexican origin. Clarifications for Spanish speakers from other countries were provided, as needed.

**Demographics.** Caregivers completed a demographics form at baseline and an updated form at 15 months. Information was collected about youth (age, gender, grade, race, ethnicity, birth order, medical history), their caregiver, and family socioeconomic status (caregiver age, sex, relationship to child, marital status, occupation, educational background, and income). Due to the numerous developmental milestones that occur between the ages of 7 years and 19 years, developmentally appropriate age groups were examined. These age groups included: pre-adolescence (7–9.99 years), early-middle adolescence (10-14.99 years), and middle-late adolescence (15-19 years). Baseline demographics were utilized in the current study.

**Medical Characteristics and Prescribed Medical Treatment**. Medical charts were reviewed at quarterly intervals (baseline, 3, 6, 9, 12, and 15 months) using standardized forms to

obtain information. Data collected included information on prescribed treatment regimens: medication type, dose, and timing of administration. It is notable that 6MP is only available in 50mg pills. As such, dosage provides us with a proxy measure for pill count and, consequently, pill burden. Prescribed medical treatment was standardized across all sites based on treatment protocols for ALL and LBL implemented by the Children's Oncology Group (COG), which facilitated data collection across each site. Information regarding the prescribed treatment regimen was used to operationalize nonadherence (e.g., discrepancy between the daily dosage of 6MP versus what had been taken by the patient as measured by electronic monitoring). Similar procedures have been used in previous research studies of adherence (Hommel et al., 2018; Quittner et al., 2000; Rapoff & Calkins-Smith, 2020; Rohan et al., 2010, 2013).

**Electronic Monitoring of 6MP.** An electronic monitoring device (i.e., the Medication Event Monitoring System (MEMS®) from the AARDEX Corporation, Palo Alto, CA) was used to monitor daily adherence to 6MP oral medication across 15 months. The MEMS® system is a prescription bottle that contains a micro-electronic chip in the cap, which registers dates and times when the bottle is opened and closed. Time-stamped medication events were stored in the MEMS® device and transferred to a program (i.e., PowerView) that records the daily history of medication taking. This information can be exported to statistical programs for analysis.

Patients and families were aware of adherence monitoring but were not given feedback regarding their medication adherence. Patients and families were instructed to take their 6MP only from the MEMS® bottle for the duration of the study, not to open the bottle unless they are taking a dose of medication at that time, and to close the bottle immediately after removing the prescribed dose. A standardized form was used during each download to capture information regarding extra openings, refills, and periods of nonuse during the previous three-month period. Adherence was defined as the number of times that oral medication was taken as prescribed

(Hommel et al., 2018; Lau et al., 1998). Electronic monitoring of oral medication usage has been used by several investigators to study medication adherence in a range of pediatric chronic illnesses (Hommel et al., 2018; Rapoff, 2010; Rapoff & Calkins-Smith, 2020; Wu et al., 2013), including ALL and LBL (Kondryn et al., 2009; Lau et al., 1998; Rohan et al., 2017; Rohan, Drotar, et al., 2015). Past work evaluating group based trajectory modeling for the current sample identified three distinct trajectories of adherence for 131 youth in the sample (Rohan, Drotar, et al., 2015). As such, the analytic sample for adherence group differences was 131 at baseline.

During the quarterly MEMS downloads, research assistants collected information from patients and families about difficulties with using the MEMS cap, including any difficulties that were experienced when using the MEMS cap as a proxy to an already established medication administration system such as a pill box. Families who used the MEMS Cap with an already established medication administration system were asked to open the MEMS cap each time that medication was removed from the other medication administration system. Electronic monitoring data for families in either group who indicated difficulties with using the MEMS cap were coded as a "non-monitored period" (i.e., missing data as this period did not reflect adherence or nonadherence patterns). Families in either group who indicated that they opened the MEMS device each time that a pill was ingested or removed from a medication bottle or pill box were included in all data analyses. Electronic monitoring data for patients and families who had periods of nonadherence but did not indicate difficulties with using the MEMS cap were included in the analyses and data was captured as true nonadherence. Patients and families who opted to use a pill box system to limit existing difficulties they were having with taking medication as prescribed were permitted to do so. The medical team corroborated reports of nonadherence difficulties. Given information regarding established patterns of nonadherence for proxy users and the level

of quality control in place for electronic monitoring data, the electronic monitoring data reflected here is likely an accurate representation of adherence rates over time. Thus, MEMS user type was not included as a covariate in data analyses.

**Quality of Life**. Health-related quality of life (HRQoL) was assessed using the 27-item, modular instrument, PedsQL 3.0 Cancer Module (Varni et al., 2002). There are three age-specific versions: young child (5-7), child (8-12), and teen (13-18). Caregiver-proxy and children/teen self-reports were collected via paper-pencil format at baseline, 6 months, and 15 months. At those same timepoints, younger children (7 years) were administered the PedsQL 3.0 Cancer Module via a standardized interview format conducted by research assistants (Appendix A); the interview scale was consistent with the standard format for administration. The PedsQL 3.0 Cancer Module was specifically designed to measure HRQoL in pediatric cancer populations. These measures assess total HRQoL and 8 separate domains of HRQoL. In addition to total HRQoL scores, the Nausea subscale domain was utilized in this study. Items include: ' I become sick to my stomach when I have medical treatments,' 'I feel too sick to my stomach to eat.' Responses were recorded on a Likert scale ranging from (0) *never a problem* to (4) *almost always* a problem, for caregiver-proxy and adolescent self-report measures. Young child (7 years) interview responses were anchored from (0) *not at all* to (2) *a lot*, using smiley faces (Appendix B). Scores were transformed to a 0–100 scale, with higher scores indicating more positive HRQoL. Cronbach's alpha for whole sample, Latinx sample, and non-Latinx sample, at baseline, 6 months, and 15 months are presented in *Table 3*.

**Beliefs about Medication.** The BAMS is a 59-item scale that asks respondents to rate, on a 7-point Likert scale, how much they agree or disagree with statements about their illness and its treatment. The BAMS was administered to youth at baseline, 6 months, and 15 months to assess beliefs about medication over time. Younger children (<11 years) were administered the

BAMS through an interview format (Appendix C) with research assistants utilizing visual aids (i.e., smiley faces) to anchor responses (Appendix D). Adolescents (≥11 years) completed the BAMS independently via paper-pencil format. The endpoint anchors of the scale were (1) *strongly disagree* and (7) *strongly agree*, except for four intent items, which had the anchors of (1) *definitely not likely* and (4) *definitely likely*. The BAMS included four subscales: Perceived Threat (PT; e.g. 'I do not think my illness is a serious illness'), Positive Outcome Expectancy (POE; e.g. 'If I take my medicine the way the doctors say I should, it helps keep me feeling well'), Negative Outcome Expectancy (NOE; e.g. 'The side effects of my medicine are so bad that I do not want to take it'), and Intent to Adhere (IA; e.g. 'I want to take every dose of my medicine the way the doctor says I should'). Lower scores on the NOE and PT subscales reflect fewer adherence barriers. Higher scores on POE and IA subscales reflect fewer adherence barriers. Subscale scores were utilized when examining patients' beliefs about medication. Cronbach's alpha for whole sample, Latinx sample, and non-Latinx sample, at baseline, 6 months, and 15 months are presented in *Table 3*.

**Depressive Symptoms of Patients and Caregivers.** Depressive symptoms were assessed with the Children's Depression Inventory (CDI; patients) and Beck Depression Inventory (BDI; caregivers) at baseline, 6 months, and 15 months. The CDI is a 27-item, reliable and valid youth self-report measure (Kovacs, 1992) that has been used to successfully identify depression in clinical samples of children and adolescents diagnosed with a chronic illness and referred from medical specialty clinics (Shemesh et al., 2005). Each item offers three sentence response options, unique to each item, which are scored as 0, 1, or 2. As such, total raw scores range from 0 to 54, with higher scores reflecting greater levels of depression. CDI raw scores of ≥11 are often used as a predetermined cutoff suggesting significant symptoms (Germann et al., 2014; Shemesh et al., 2005). Standardized T-scores, based on population norms (Kovacs, 1985,

1992), were used for descriptive analyses, consistent with past work in pediatric cancer populations (Germann et al., 2014). Cronbach's alpha for whole sample, Latinx sample, and non-Latinx sample, at baseline, 6 months, and 15 months are presented in *Table 3*.

The Beck Depression Inventory (BDI), a 21-item self-report rating inventory, was used to measure caregiver symptoms and attitudes characteristic of depression (Beck et al., 1961). Respondents are asked to select the statement in each item group that best describes how they have been feeling in the past week, including today. Each item offers 4 sentence response options, which are scored 0, 1, 2, or 3. Total scores range from 0 to 63. Scores higher than 20 indicate a clinical level of depression. Cronbach's alpha for whole sample, Latinx sample, and non-Latinx sample, at baseline, 6 months, and 15 months are presented in *Table 3*.

**Parent-Adolescent Communication and Conflict.** The Parent-Adolescent Conflict Scale (PAC), a brief version of the Issues Checklist (IC; Robin & Foster, 1989) was completed by children and caregivers separately at baseline, 6 months, and 15 months. The PAC assessed general family communication by asking about 15 issues commonly discussed in adolescence (e.g., which friends they can spend time with, what they can watch on television, chores around the house). For each issue, the respondent was asked whether the issue was discussed in the past 2 weeks and if so, how many times the issue was discussed and how intense the discussions were. Frequency of communication was recorded on a 4-point Likert scale from (1) not often to (4) very often. For this study, a total frequency value was derived by totaling discussion frequency scores across the 15 items. Possible total discussion frequency values ranged from 0 (no items discussed) to 60 (every item discussed very often). Not discussing an item was coded as 0. Intensity (or level of conflict) was reported on a 5-point Likert scale from (1) calm to (5) very angry. Mean intensity was computed by dividing the frequency total by the number of issues discussed, to assess average conflict across issues. Total discussion frequency Cronbach's

alphas for whole sample, Latinx sample, and non-Latinx sample, at baseline, 6 months, and 15 months are presented in *Table 3*. Cronbach's alphas could not be calculated for the mean intensity subscale given the variability in the number of items discussed between individual respondents.

**Quality Control of Data Used in the Proposed Study.** All study data was sent to CCHMC (the Central Coordinating Site) and was cleaned by research coordinators in Cincinnati under the supervision of J. Rohan. Electronic monitoring data was reviewed for quality and data integrity and issues were addressed with specific site personnel. Electronic monitoring data was stored in a secured database and double-checked for accuracy.

## Data Analytic Plan

See *Table 1*, which provides a summary of the analyses that were conducted for Aims 1-3, including the aims/hypotheses, data analytic methods, and purpose of each analysis.

**Aim 1: Describe Characteristics of Medication Adherence Subgroups.** As described in prior research conducted by Rohan and colleagues (Rohan, Drotar, et al., 2015; Rohan & Geaney, 2018), three adherence trajectories were identified within this cohort at both baseline and 15-months using Latent Group-based Trajectory Modeling (LGTM) approaches (Jones et al., 2001; Jones & Nagin, 2007; Nagin, 2005; Rohan et al., 2015): optimal adherence, moderate adherence, and chronic nonadherence. Behavioral adherence trajectories across 15-months are described in *Figure 1*. *Table 4* provides LGTM model estimates for each trajectory group. As shown in *Figure 1*, the majority of patients ($n$ = 88, 67.1 %) demonstrated exemplary adherence rates across 15 months: starting at 96.3% (week 1) and decreasing at a rate of -0.10% per week; such that at 15 months behavioral adherence was 94.8%. A second, smaller, group ($n$ = 26, 20%) demonstrated poor adherence at the start of monitoring based on electronic monitoring data (67.6% at week 1), which remained relatively stable over time, decreasing at a rate of -0.01% to

an average of 67.5% at 15 months. The third and smallest group ($n$ = 17, 12.9%) never established an adequate pattern of behavioral adherence with adherence levels of only 62.7% at baseline and decreasing at a rate of -2.8% per week; such that at 15 months adherence was approximately 30%. To address Aim 1, description of individual- and family-level characteristics across the three medication adherence subgroups, descriptive statistics were run for demographic and medical data as well as individual- and family-level factors across the three groups. Here, means, standard deviations, and ranges for continuous demographic and criterion variables were calculated. For categorical demographic and criterion variables, percentages were examined (see Tables 2 and 5).

**Preliminary Analyses for Aims 2 and 3:** Clinically-relevant demographic and medical characteristics were compared across the two groups (adherent and nonadherent) using correlations, independent t-tests (continuous variables), or chi-squares (categorical variables) to determine which demographic and medical variables, if any, should be included as covariates in statistical models described in Aims 2-3 (see *Table 2b* and *Table 6*). Normality distributions and homogeneity of variance were examined (as relevant) for all continuous variables included in this study. Generalized linear models were used for categorical outcomes, which are appropriate for both normal and non-normal distributions. Based on prior research (Bhatia, 2011; Bhatia et al., 2012; Davies & Lilleyman, 1995), the following covariates were examined: patient gender, patient age, patient ethnicity/race, single caregiver versus two caregiver households, diagnosis duration, and 6MP dose.

Results of the randomized controlled trial indicated that there were no significant differences in behavioral medication adherence between those patients who participated in the family-centered problem-solving intervention compared to those who received clinical care as usual ($p$ = 0.12, d = 0.21; Ko et al., 2021; Rohan, 2014). However, given the potential

importance of group membership on relevant psychosocial and health outcomes for individual patients, RCT group was explored as a possible covariate in preliminary analyses for Aims 2-3.

**Aim 2a: Identification of Predictors of 6MP Medication Adherence.** Aim 2a examined whether individual- and family-level factors (e.g., baseline number of younger siblings/children in home and sibling age group, longitudinal health beliefs, child and caregiver depression, and caregiver-child communication) predicted 6MP adherence group membership. To account for collinearity and shared variance between caregiver- and child-reported communication, two separate models were run: one including child-reported communication and the second including caregiver-reported communication. The primary analysis utilized longitudinal mixed effects models to examine whether the above individual- and family-level factors predicted 6MP medication adherence subgroups (adherent vs. nonadherent), as measured by electronic monitoring. Generalized linear mixed effects models (mixed effects longitudinal logistic regression) were used to identify predictors of medication adherence group (adherent versus nonadherent). The GENMOD procedure in SAS 9.4 was utilized as this procedure uses an iterative fitting process to fit a generalized linear model to the data using maximum likelihood estimations (Johnston, 1993). This procedure is suitable for outcome variables with both normal and non-normal distributions. Working correlation structures were examined for all models (e.g., unstructured vs structured vs exchange; child vs parent) and the "best fit" models were chosen using the appropriate model fit statistics (e.g., AIC, QIC, QICu values, which are dependent on the model type used for the analysis; Cui, 2007; Vaida & Blanchard, 2005). Fit statistics are used to compare models against one another, with the smallest value indicating the best fitting model (Cui, 2007; Pan, 2001). Analyses were conducted with SAS 9.4 and SPSS 28. See *Table 1*, which provides a summary of the analyses conducted for Aim 2a.

**Aim 2b (Exploratory Analyses): Examine Potential Between Group Differences of Predictors of 6MP Medication Adherence.** Aim 2b examined whether the individual- and family-level factors (number of younger siblings/children in home, health beliefs, and child and caregiver depression) that predicted 6MP adherence patterns (adherent vs. nonadherent) varied across Latinx and non-Latinx, white children (*Table 2b*). The primary analysis utilized generalized longitudinal binomial logistic regression to examine whether the above individual- and family-level factors that predicted 6MP medication adherence subgroup, as measured by electronic monitoring, differed across ethnic groups (Latinx vs. non-Latinx, white children). Given the exploratory nature of these analyses and the lack of directional hypotheses, Bonferroni corrections were evaluated for these analyses. Analyses were conducted with SPSS 28. See *Table 1*, which provides a summary of the analyses conducted for Aim 2b.

**A Priori Power Analysis.** Using past work that investigated the relationship between individual- and family-level factors and medication adherence/health outcomes in pediatric cancer and pediatric type 1 diabetes (Rohan et al., 2017; Rohan, Drotar, et al., 2014, 2015; Rohan, Huang, et al., 2014; Rohan, Rausch, et al., 2015), a total sample size of 109 patients was needed for the univariate and multivariate analyses to yield at least 90% power for the analyses proposed in Aims 2a and 2b.

**Aim 3 (Exploratory Analyses): Examine the Bidirectional Relationship Between Adherence and Quality of Life.** Aim 3 included exploratory analyses examining the bidirectional relationship between 6MP adherence subgroups and quality of life. The analyses utilized both general linear mixed models for normal/continuous outcomes (mixed ANOVA) and generalized linear mixed effects models for non-normal/categorical outcomes (mixed effects longitudinal logistic regression) to examine bi-directional relationships between 6MP medication adherence and quality of life (total quality of life score, nausea quality of life score).

To account for collinearity between child- and caregiver-reported quality of life responses, a separate child-reported model and caregiver-reported model was evaluated.

**A Priori Power Analysis.** Using prior research from the current parent study investigating the relationship between medication adherence and quality of life (Bolden & Isaac, 2020), a sample size of 109 patients was needed to yield at least 90% power for the proposed Aim 3 analyses that examined the bi-directional relationship between 6MP adherence and QoL.

## Results

A description of the data analytic methods utilized to examine Aims 1-3, and their associated hypotheses, are presented in *Table 1*.

### Aim 1: Description of characteristics for each of the three adherence group trajectories across 15-months in a cohort of pediatric cancer patients

**Demographic and Medical Characteristics.** Descriptive statistics for the study's baseline variables are presented in *Table 2a*. Characteristics were evaluated for the full sample ($N$ = 139) and those in the three adherence trajectory groups ($n$ = 131). We hypothesized that youth in the moderate adherence and chronic nonadherence groups would be older than youth in the optimal adherence group. This hypothesis was partially supported. While youth in the optimal adherence group were found to be significantly younger than those in the moderate adherence group ($M_{diff}$ = 1.83 years, $p$ = 0.04) at baseline, youth in the chronically nonadherent group were not significantly older than youth in the optimal adherence group ($M_{diff}$ = 1.60 years, $p$ = 0.179) at baseline. There were no significant differences across the groups with respect to baseline: patient gender, education, ethnicity, number of kids in the home, caregiver gender, caregiver marital status, income, household composition (one versus two caregiver home), or whether there were older kids present in the home ($p$ > 0.05). However, results did indicate that youth in the chronically nonadherent group were more likely to have younger kids present in the

home at baseline compared to youth in the optimal and moderate adherence groups, $\chi^2$ (1, 130) = 9.82, $p$ = 0.007.

With respect to medical characteristics, the majority of patients in this sample were diagnosed with ALL (96%). Four percent of patients were diagnosed with LBL. Time since diagnosis at baseline did not significantly differ across the three adherence groups ($p$ = 0.64). We hypothesized that 6MP dosage (i.e., a proxy to pill burden) would vary across the three adherence groups, with youth in the optimal adherence group having the lowest 6MP dose (which equates to taking less total oral pills in a single administration (i.e., less pill burden as 6MP pills only come in 50mg increments), youth in the moderate adherence group having the second lowest dose, and youth in the chronic nonadherence group having the highest dose (which equates to taking the most total daily 6MP 50mg pills in a single administration (i.e., high pill burden)). This hypothesis was partially supported (see *Table 5*). Specifically, youth in the optimal adherence group were prescribed significantly lower doses of 6MP than those youth in the moderate adherence group at baseline (~1.5 pills vs. >2 pills), 6 months (~1.5 pills vs. >2 pills), and 15 months (~2 pills vs. >2.5 pills; $p < 0.05$). However, youth in the chronically nonadherent group did not have significantly higher doses of 6MP compared to youth in the moderately adherent group ($M_{diff}$ = 7.56 mg, $p > 0.05$). In fact, youth in the chronically nonadherent group were prescribed significantly lower 6MP doses at baseline compared to youth in the moderate adherence group at baseline ($M_{diff}$ = 28.94 mg, $p < 0.05$). Dosage did not significantly differ between the moderate adherence group and chronically nonadherent group at 6- or 15-months ($p > 0.05$). Additionally, dosage did not significantly differ for youth in the optimal adherence or chronically nonadherent groups at baseline, 6-, or 15-months ($p > 0.05$).

**Individual and Family Level Factors.** Group comparisons of additional individual- and family-level factors were exploratory (*Table 5*). Evaluation of child-reported depressive

symptoms revealed that very few youth ($n$ = 4) in the present study reported T-scores indicating clinically significant levels of depressive symptoms at baseline ($n$ = 2), 6 months ($n$ = 2), or 15 months ($n$ = 2). At each time point, only 1.4% of youth reported clinically significant levels of depression. The mean CDI total raw scores ranged from 0.9 to 2.0 (out of a possible 54) across groups and time points. Neither raw CDI nor CDI T-scores differed across the groups ($p > 0.05$). Conversely, approximately 10% of caregivers reported clinically significant levels of depressive symptoms on the BDI at baseline, 6 months, and 15 months. However, neither mean BDI score nor percentage of caregivers reporting clinically significant levels of depressive symptoms significantly differed across the three adherence groups ($p > 0.05$).

Child- and caregiver-reported communication and conflict were also compared across the three groups. Child-reported total communication frequency did not significantly differ between the three adherence groups at baseline or 6 months ($p > 0.05$). However, at 15-months, youth in the chronically nonadherent group reported having significantly less discussions with their caregivers ($M$ = 6.1, $SD$ = 4.8) than youth in the optimal adherence group ($M_{diff}$ = 7.7, $F(2, 113) = 4.1$, $p = 0.017$). Average child-reported conflict also did not significantly differ across subgroups at baseline, 6 months, or 15 months ($p > 0.05$). Finally, results did not indicate significant differences in caregiver-reported total communication frequency or average conflict at baseline, 6 months, or 15 months ($p > 0.05$).

Youth-reported beliefs about medication were also evaluated across groups and time points. Youth in the optimal adherence group reported higher positive outcome expectancy (e.g., 'If I take my medicine the way the doctors say I should, it helps keep me feeling well') at baseline compared to youth in the moderate adherence group ($M_{diff}$ = 8.0, $p$ = 0.031). Positive outcome expectancy ratings did not vary between the optimal adherence group and the chronically nonadherent group nor the chronically nonadherent group and moderately adherent

group ($p > 0.05$). Further, there were no significant differences across groups with respect to: perceived threat, negative outcome expectancy, or intention, at baseline, 6 months, or 15 months ($p > 0.05$).

**Preliminary Analyses Aims 2a and 2b**

Normality and homogeneity of variance criteria were met as relevant. Due to the small sample sizes of both the chronic nonadherence ($n = 17$) and moderate adherence ($n = 36$) subgroups relative to the optimal adherence subgroup ($n = 88$), the chronic nonadherence group and the moderate adherence group were combined into a single subgroup, referred to as the "nonadherent group," for all analyses discussed in Aims 2-3. The optimal adherence group was referred to as the "adherent group." Based on prior research (Bhatia, 2011; Bhatia et al., 2012; Davies & Lilleyman, 1995; Rohan et al., 2017; Rohan, Drotar, et al., 2015; Rohan & Winter, 2021), the following covariates were examined for inclusion in analyses, baseline: patient age group (pre-adolescence: 7-9.99 years, early-middle adolescence: 10-14.99 years, middle-late adolescence: 15-19 years), patient gender, patient ethnicity and race, single caregiver versus two caregiver households, maternal education, household income, and diagnosis duration (*Table 2a* and *Table 6*). Results indicated that age group (*Figure 2*) and 6MP dosage (at baseline, 6 months, and 15 months, *Figure 3*) were significantly related with adherence group membership in the full sample. All other demographic and medical characteristics were not significantly related to adherence group membership in the full sample. As such, baseline age group and longitudinal 6MP dosage were added as covariates into predictive models for Aim 2a.

Results of the randomized controlled trial indicated that there were no significant differences in behavioral medication adherence between patients who participated in the family-centered problem-solving intervention compared to those who received clinical care as usual ($p = 0.12$, $d = 0.21$; Rohan et al., 2017). Nevertheless, given the potential influence of group

membership on individual- and family-level factors, group membership was examined as a potential covariate in preliminary general linear models. These preliminary analyses did not indicate that RCT group membership was significantly related to adherence trajectory group membership (*Table 6*). As such, RCT group membership was not included as a covariate in predictive models for Aims 2a or 2b.

Alternative competing models were examined for Aim 2a to determine which specific predictor variables should be included in the final comprehensive predictive model. Predictor variables that were significantly related to adherence group membership in preliminary analyses; or, had a theoretical rationale based on prior research, were included in the final predictive models. It is notable that child-reported depressive symptoms, caregiver-reported depressive symptoms, and child- and caregiver-reported conflict scores were not included in final predictive models given the limited range and variability of scores for these measures and the lack of statistical significance found in preliminary analyses. Finally, all competing models were examined based on best fit statistics for each model and the models with the best statistical fit were chosen as the final predictive model. Baseline patient age group and number of younger children in the household, and longitudinal dosage, beliefs about medication (POE, Intent, NOE), and caregiver-child communication were retained as predictor variables in Aim 2a analyses.

**Aim 2a. Identifying predictors of 6MP medication adherence group (adherent versus nonadherent) in a cohort of pediatric cancer patients**

Generalized linear mixed effects models (mixed effects longitudinal logistic regression) were used to examine predictors of medication adherence group membership (adherent versus nonadherent). Given preliminary analyses indicating that child-reported depressive symptoms, caregiver-reported depressive symptoms, and child-/caregiver-reported conflict were not significantly related to medication adherence group membership in univariate analyses,

hypotheses regarding the relationship between these predictor variables and medication adherence group membership are considered unsupported. Thus, Aim 2a analyses focused on whether developmental phase, number of younger children in the home, beliefs that negative or positive outcomes would occur from taking medication, adherence intent, 6MP dosage, or caregiver- or child-reported communication patterns predicted risk for nonadherence (*Table 2b*). To account for collinearity and shared variance between caregiver- and child-reported communication patterns, two separate models for child- and caregiver-report were separately examined (*Table 7*): one including only child-reported communication and the second including only caregiver-reported communication, which is similar to other predictive models investigating health outcomes in pediatric chronic illness (Rohan, Huang, et al., 2014).

**Child-Reported Communication Model.** As hypothesized, when controlling for all other factors, developmental phase was significantly related to increased risk of nonadherence ($p = 0.007$; see *Tables 2b* and *7*). Pre-adolescents were 0.25 times less likely ($\beta = -1.38$) to be in the nonadherent group than youth in the middle-late adolescent age group. Similarly, early-middle adolescents were 1.44 times less likely ($\beta = -0.37$) to be in the nonadherent subgroup compared to middle-late adolescents. Additionally, as hypothesized, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR: 1.0, $p = 0.02$, see *Figure 3*). In contrast, when controlling for all other factors, the number of younger kids in the home ($p = 0.50$, see *Table 7*), NOE ($p = 0.18$, see *Figure 4*), POE ($p = 0.08$, see *Figure 5*), Intent ($p = 0.07$, see *Figure 6*), nor child-reported total communication frequency ($p = 0.29$, see *Figure 7*) significantly predicted nonadherence risk. The child-reported communication mode had a model fit statistic (QICu) of 435.67.

**Caregiver-Reported Communication Model.** Consistent with the child-reported communication model, as hypothesized, when controlling for all other factors in the caregiver-

reported model, developmental phase also was significantly related to increased risk of nonadherence ($p = 0.008$; see *Tables 2b* and *7*). Pre-adolescents were 0.24 times less likely ($\beta = -1.44$) than middle-late adolescents to be nonadherent. Those in early-middle adolescence were 1.61 times less likely ($\beta = -0.48$) to be in the nonadherent group than those in middle-late adolescence. Additionally, as hypothesized, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR = 1.0, $p = 0.04$, see *Figure 3*). In contrast to the child model, when controlling for all other factors, youth who reported higher outcome expectancies were less likely to be nonadherent (OR: 1.0, $p = 0.02$, see *Figure 5*). Indicating that youth who expected fewer positive outcomes from taking their medication were at an increased risk of being nonadherent. Moreover, similar to the child-reported model, when controlling for all other factors, number of younger kids in the home ($p = 0.34$), NOE ($p = 0.16$), Adherence Intent ($p = 0.19$), and caregiver-reported total communication frequency ($p = 0.12$, see *Figure 8*) did not significantly predict increased risk of nonadherence. With caregiver-reported communication entered in the model, model fit (QICu) was 379.2, indicating that caregiver-reported communication was a better predictor than child-reported communication based on model fit statistics (Hardin & Hilbe, 2012).

In order to further understand the relationship between age group and the remaining independent variables, exploratory one-way ANOVA analyses and an additional linear regression were conducted. Results of these exploratory analyses indicated significant differences between age groups across several domains (*Table 8*). Particularly notable was the significant positive relationship between age group and 6MP daily dosage. Specifically, a one-unit increase in age group at baseline was associated with a 70.7mg increase in 6MP dosage at baseline ($F(1, 137) = 20.32$, $R^2 = 0.13$, $p < 0.001$), a 74.6mg increase in dosage at 6 months ($F(1, 131) = 27.57$, $R^2 = 0.17$, $p < 0.001$), and a 90mg increase in dosage at 15 months ($F(1, 108) =$

32.01, $R^2 = 0.22$, $p < 0.001$). Indicating that older adolescents were prescribed significantly higher doses of 6MP than younger youth.

**Aim 2b. Exploratory Analyses: Examine between group differences of predictors of 6MP medication adherence (adherent vs nonadherent) in a cohort of pediatric cancer patients**

Aim 2b explored potential between group differences of predictors of 6MP medication adherence group membership. As such, analyses focused on two subsamples: (1) Latinx patients ($n = 47$) and (2) non-Latinx, white patients ($n = 76$). In order to determine which predictors to include in predictive analyses, descriptive statistics were run for demographic and medical data as well as individual- and family-level factors across the two adherence groups (adherent vs nonadherent; *Table 2b*). For these analyses, means, standard deviations, and ranges for continuous demographic and criterion variables were calculated. For categorical demographic and criterion variables, percentages were examined. A total of two cross sectional and seven longitudinal t-tests were run within each subsample. As such, Bonferroni corrections indicated a necessary *p* value of 0.006 at each timepoint to reject the null hypothesis (R. A. Armstrong, 2014).

***Latinx Patients***. Comparisons of demographic factors indicated no significant differences between the Latinx youth in the nonadherent and adherent groups with respect to baseline: patient gender, age, maternal education, number of people in the home, caregiver gender, caregiver marital status, income, household composition (one versus two caregiver home), or whether there were younger or older children present in the home ($p > 0.05$). With respect to medical characteristics, time since diagnosis at baseline did not significantly differ across the adherence groups ($p = 0.55$; *Table 2b*). Conversely, 6MP dose differed between the two groups at baseline and 15 months. Specifically, Latinx youth in the adherent group were prescribed lower doses of 6MP than Latinx youth in the nonadherent group at baseline ($M_{diff} = 33.5$, $t(43) =$

2.28, $p = 0.03$, Bonferroni $p > 0.006$) and 15 months ($M_{diff} = 45.9$, $t(32) = 2.63$, $p = 0.01$, Bonferroni $p > 0.006$); however, these differences did not remain significant when examining the Bonferroni corrected $p$ value. Dosage did not significantly differ between the two groups at 6 months ($p = 0.14$).

Analyses examining individual- and family-level factors revealed no significant differences between the adherence groups' mean caregiver-reported depression, child-reported total communication, caregiver-reported total communication, and several domains of health beliefs (i.e., negative outcome expectancy, perceived threat, intention). Results did, however, indicate that Latinx youth in the adherent group reported higher positive outcome expectancy at baseline (e.g., 'If I take my medicine the way the doctors say I should, it helps keep me feeling well') than youth in the nonadherent group ($M_{diff} = 9.0$, $t(43) = -2.35$, $p = 0.02$, Bonferroni $p > 0.006$); however, these differences did not remain significant when examining the Bonferroni corrected $p$ value. Child-reported positive outcome expectancy did not significantly differ at 6- or 15-months ($p > 0.05$).

Given these preliminary analyses, only 6MP dose and positive outcome expectancy were retained as possible predictors of adherence among Latinx youth in Aim 2b analyses. To conserve power in our predictive analyses, 6MP dose and positive outcome expectancy were examined in two separate longitudinal binomial logistic regressions.

**6MP Dose.** A longitudinal logistic regression analysis assessed whether 6MP dose across time significantly predicted adherence group membership among Latinx youth. A test of the full model against the constant only model was significant, $\chi^2$ (3) = 7.91, $N = 47$, $p = 0.048$, Nagelkerke $R^2 = 0.30$, indicating that 6MP dose significantly differed over time between those who were in the adherent group versus those in the nonadherent group. Specifically, Latinx youth with higher 6MP doses were at increased risk for nonadherence. According to Wald

criterions, however, cross-sectional dose at baseline, 6 month, and 15 months did not individually predict adherence group membership ($p > 0.05$). These results indicate that investigating longitudinal patterns of 6MP dosage over time is a better predictor of adherence group membership among Latinx youth compared to investigating only a single point of time.

**Positive Outcome Expectancy.** A longitudinal logistic regression analysis assessed whether child-reported positive outcome expectancy across time significantly predicted adherence group membership among Latinx youth. A test of the full model against the constant only model was not significant, $\chi^2$ (3) = 5.69, $N$ = 47, $p$ = 0.13, Nagelkerke $R^2$ = 0.20. However, according to Wald criterions, positive outcome expectancy at baseline significantly predicted adherence group membership ($p$ = 0.04). Specifically, the change in odds associated with one-unit change in reported positive outcome expectancy (at baseline) was 0.086, indicating that higher reported positive outcome expectancy at baseline increased likelihood of adherent group membership. Thus, in this model, baseline positive outcome expectancy was a better predictor of adherence group membership among Latinx youth than positive outcome expectancy over time.

***Non-Latinx, white Participants.*** Comparisons of demographic factors (*Table 2b*) indicated that non-Latinx, white (hereafter referred to as white) youth in the nonadherent group were more likely to be older than those in the adherent group, $\chi^2$ (2, 71) = 6.86, $p$ = 0.03, at baseline. There were more youth in middle-late adolescence in the nonadherent group (42%) compared to the adherent group (19%). Youth in the adherent group were more likely to be in pre-adolescence (51%) compared to older peers who were more likely to be in the nonadherent group (21%). Comparisons of additional demographic factors indicated no significant differences between the white youth in the nonadherent and adherent groups with respect to baseline: patient gender, maternal education, number of people in the home, caregiver gender, caregiver marital status, income, household composition (one versus two caregiver home), or whether there were

younger or older children present in the home ($p > 0.05$). With respect to medical characteristics, time since diagnosis did not significantly differ across the two adherence groups ($p = 0.51$). Conversely, 6MP dose significantly differed between the groups at baseline and 15 months. Specifically, white youth in the adherent group were prescribed lower doses of 6MP than white youth in the nonadherent group at baseline ($M_{diff} = 21.2$, $t(69) = 2.62$, $p = 0.01$, Bonferroni $p > 0.006$) and 15 months ($M_{diff} = 23.2$, $t(56) = 2.06$, $p = 0.04$, Bonferroni $p > 0.006$); however, these differences did not remain significant when examining the Bonferroni corrected $p$ value. Dosage did not significantly differ between the two groups at 6 months ($p = 0.32$).

Analyses examining individual- and family-level factors revealed no significant differences between the groups' mean caregiver reported depression nor health beliefs domains of negative outcome expectancy, perceived threat, intention, or positive outcome expectancy. Conversely, results indicated that white youth in the adherent group reported higher communication frequency at 15 months than youth in the nonadherent group ($M_{diff} = 5.6$, $t(59.1) = -2.6$, $p = 0.01$; Bonferroni $p > 0.006$); however, this difference did not remain significant when examining the Bonferroni corrected $p$ value. Moreover, white caregivers whose children were in the adherent group reported more frequent communication at 6 months ($M_{diff} = 5.8$, $t(60.1) = -2.4$, $p = 0.019$; Bonferroni $p > 0.006$) and 15 months ($M_{diff} = 8.0$, $t(48.7) = -3.3$, $p = 0.002$; Bonferroni $p < 0.006$); however, these differences only remained significant at 15 months when examining the Bonferroni corrected $p$ value. Additionally, caregivers in the nonadherent group reported significantly greater caregiver-child conflict at baseline than parents in the adherent group ($M_{diff} = 0.35$, $t(62) = 2.9$, $p = 0.005$; Bonferroni $p < 0.006$). Youth in the adherent and nonadherent groups did not report significantly different levels of caregiver-child conflict.

Given these preliminary analyses, baseline age group and longitudinal child-reported total communication frequency, caregiver-reported total communication frequency, and 6MP

dose were retained as possible predictors of adherence among white youth in Aim 2b analyses. As in Aim 2a analyses, caregiver-reported communication conflict was not included in predictive models, as this measure's Cronbach's alpha could not be assessed due to small sample size. In order to conserve power in our predictive analyses, separate binomial logistic regressions were run for each predictor.

**Age Group.** A logistic regression analysis assessed whether age group (at baseline) significantly affected whether white children were in the nonadherent or adherent group. A test of the full model against the constant only model was significant, $\chi^2(1) = 6.82$, $N = 76$, $p = 0.009$, Nagelkerke $R^2 = 0.13$. According to Wald criteria, age group at baseline significantly predicted whether white youth were in the adherent versus nonadherent group. Specifically, youth in the pre-adolescence and early-middle adolescence age groups were less likely to be in the nonadherent group than youth in the middle-late adolescence age group. With a one-unit increase in age group, the odds of being in the adherent group decreased by –0.83 ($p = 0.012$). Indicating that white youth in the middle-late adolescent age group were most likely to be in the nonadherent group. Thus, being in an older age group at baseline decreased the likelihood of adherent group membership among white youth.

**6MP Dose.** A longitudinal logistic regression analysis assessed whether 6MP dose across time significantly predicted adherence group membership among white youth. A test of the full model against the constant only model was significant, $\chi^2(3) = 8.71$, $N = 76$, $p = 0.03$, Nagelkerke $R^2 = 0.20$, indicating that longitudinal dose significantly predicted adherence group membership. Moreover, according to Wald criterions, baseline dosage significantly predicted adherence group membership ($p = 0.04$). Specifically, the change in odds associated with one-unit change of dose (at baseline) was -0.21, indicating that a higher 6MP dose at baseline decreased likelihood of adherent group membership. Thus, in this model, both cross-sectional

baseline dose and dosage over time significantly predicted adherence group membership among white youth. These findings indicated that 6MP dosage prescribed at baseline accounted for more of the variance in longitudinal adherence behaviors than dosage at 6 month or 15 month.

**Child-Reported Communication Frequency.** A longitudinal logistic regression analysis assessed whether child-reported total communication frequency across time significantly predicted adherence group membership among white youth. A test of the full model against the constant only model was significant, $\chi^2(3) = 8.28$, $N = 76$, $p = 0.04$, Nagelkerke $R^2 = 0.17$. Higher levels of child-reported communication frequency was associated with decreased risk of nonadherence. However, Wald criteria indicated that none of the cross-sectional child-reported total communication scores significantly predicted adherence group membership ($p > 0.05$). Thus, longitudinal child-reported communication was significantly better at predicting adherence group membership in this model than cross-sectional child-reported communication frequency at baseline, 6 months, or 15 months. Indicating that the pattern of child-reported communication over time was more predictive of adherence behavior than communication at any isolated timepoint.

**Caregiver-Reported Communication Frequency.** A longitudinal logistic regression analysis assessed whether caregiver-reported total communication frequency across time significantly predicted adherence group membership among white youth. Similar to the child-reported model, a test of the full model against the constant only model was significant, $\chi^2$ (3) = 9.77, $N = 76$, $p = 0.02$, Nagelkerke $R^2 = 0.23$. Higher levels of caregiver-reported communication frequency was also associated with decreased risk of nonadherence. However, Wald criteria indicated that none of the cross-sectional caregiver-reported total communication scores significantly predicted adherence group membership ($p > 0.05$). Thus, longitudinal caregiver-reported communication was significantly better at predicting adherence group membership in

this model than cross-sectional caregiver-reported communication frequency at baseline, 6 months, or 15 months. Similarly indicating that the pattern of caregiver-reported communication over time was more predictive of youth's adherence behaviors than communication frequency considered at any isolated timepoint.

**Overview of Differences in Predictors Between Ethnic Groups.** Exploratory analyses revealed possible between group differences with respect to predictors of medication adherence group membership (*Table 2b*). Among Latinx patients, in single factor models, longitudinal 6MP dosage and baseline positive outcome expectancy significantly predicted adherence group membership. Conversely, among white patients, single factor models indicated that baseline age group, baseline and longitudinal 6MP dose, and longitudinal child-reported and caregiver-reported communication frequency significantly predicted adherence group membership.

**Aim 3. Exploratory Analyses: Examine bidirectional predictive model of quality of life and medication adherence**

Aim 3 examined the bidirectional relationship between quality of life and 6MP adherence groups. Due to low Cronbach's alpha statistics (*Table 3*) for the PedsQL young child (5-7) form in this sample, youth under the age of 8 were excluded from Aim 3 analyses. Model fit was examined with and without youth under the age of 8. Both QIC (fit of overall model) and QICu (fit of model covariates) improved when excluding youth under the age of 8 ($M_{\text{diff}}$ = 35 and 36, respectively). As such, the analytic sample for Aim 3 consisted of 123 youth (aged 8 to 19).

Analyses included general linear mixed models when assessing factors related to HRQoL and generalized linear mixed effects models when evaluating factors that predict medication adherence group membership. To account for multicollinearity among child-reported and caregiver-reported HRQoL, separate child and caregiver models were evaluated. Additionally, separate total HRQoL and nausea HRQoL models were also evaluated to account for

multicollinearity among total HRQoL and nausea subscale values. Thus, four separate models were conducted for each outcome variable: (1) Child-reported total HRQoL, (2) Child-reported nausea HRQoL, (3) Caregiver-reported total HRQoL, and (4) Caregiver-reported nausea HRQoL.

**Adherence Group Membership as Dependent Variable.** Based on Aim 2a results, baseline age group and longitudinal 6MP dose and POE were included as covariates in the following predictive models. Based on past work (Tebbi et al., 1986) and theory (Fiese et al., 2005), number of younger kids in the home was also included as a covariate in the total HRQoL models.

**Child-Reported Total HRQoL as Predictor**. When controlling for the above-mentioned covariates, child reported total HRQoL did not significantly predict adherence group membership ($p = 0.57$). Similar to Aim 2a analyses, when controlling for all other factors, developmental phase was significantly related to increased risk of nonadherence ($p = 0.02$; see *Table 9*). Pre-adolescents were 0.28 times less likely ($\beta = -1.28$) to be in the nonadherent group than youth in the middle-late adolescent age group. Similarly, early-middle adolescents were 0.70 times less likely ($\beta = -0.36$) to be in the nonadherent subgroup compared to middle-late adolescents. Additionally, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR: 1.0, $p = 0.04$, see *Figure 3*). Moreover, when controlling for all other factors, as POE increased, the risk of being nonadherent decreased (OR: 1, $p = 0.04$, see *Figure 5*). In contrast, when controlling for all other factors, number of younger kids in the home ($p = 0.42$, see *Table 7*) did not significantly predict nonadherence risk. With child-reported total HRQoL entered in the model, the covariate model fit (QICu) was 396.6.

**Caregiver-Reported Total HRQoL as Predictor**. When controlling for the above-mentioned covariates, caregiver reported total HRQoL did not significantly predict adherence

group membership ($p$ = 0.59). Similar to Aim 2a analyses, when controlling for all other factors, developmental phase was significantly related to increased risk of nonadherence ($p$ = 0.02; see *Table 9*). Pre-adolescents were 0.28 times less likely (β = -1.28) to be in the nonadherent group than youth in the middle-late adolescent age group. Similarly, early-middle adolescents were 0.70 times less likely (β = -0.36) to be in the nonadherent subgroup compared to middle-late adolescents. Additionally, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR: 1.0, $p$ = 0.04, see *Figure 3*). Moreover, when controlling for all other factors, as POE increased, the risk of being nonadherent decreased (OR: 1, $p$ = 0.03, see *Figure X*). In contrast, when controlling for all other factors, number of younger kids in the home ($p$ = 0.42, see *Table 7*) did not significantly predict nonadherence risk. With caregiver-reported total HRQoL entered in the model, the covariate fit (QICu) was 394.2. Indicating that child- and caregiver-reported total HRQoL similarly were equally strong predictive models.

**Child-Reported Nausea HRQoL as Predictor.** When controlling for age group, positive outcome expectancy, and 6MP dose, child-reported nausea HRQoL did not significantly relate to adherence group membership ($p$ = 0.58). Similar to previous analyses, when controlling for all other factors, developmental phase was significantly related to increased risk of nonadherence ($p$ = 0.01; see *Table 9)*. Pre-adolescents were 0.26 times less likely (β = -1.36) to be in the nonadherent group than youth in the middle-late adolescent age group. Similarly, early-middle adolescents were 0.63 times less likely (β = -0.46) to be in the nonadherent subgroup compared to middle-late adolescents. Additionally, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR: 1.0, $p$ = 0.04, see *Figure 3*). Contrary to previous HRQoL models, when controlling for all other factors, POE did not

significantly predict risk of nonadherence ($p = 0.053$). With child-reported nausea HRQoL entered in the model, the covariate model fit (QICu) was 400.9.

**Caregiver-Reported Nausea HRQoL as Predictor.** When controlling for age group, positive outcome expectancy, and 6MP dose, caregiver-reported nausea HRQoL did not significantly relate to adherence group membership ($p = 0.29$). Similar to previous analyses, when controlling for all other factors, developmental phase was significantly related to increased risk of nonadherence ($p = 0.01$; see *Table 9*). Pre-adolescents were 0.26 times less likely ($\beta = -1.36$) to be in the nonadherent group than youth in the middle-late adolescent age group. Similarly, early-middle adolescents were 0.63 ($\beta = -0.46$) to be in the nonadherent subgroup compared to middle-late adolescents. Additionally, when controlling for all other factors, as 6MP dosage increased the risk of being nonadherent also increased (OR: 1.0, $p = 0.04$, see *Figure 3*). Contrary to the child-reported nausea model, when controlling for all other factors, as POE increased, the risk of being nonadherent decreased (OR: 1.0, $p = 0.04$, see *Figure X*). With caregiver-reported nausea HRQoL entered in the model, the covariate model fit (QICu) was 398.5. Indicating that both child- and caregiver-reported nausea HRQoL were equally strong predictive models.

It was hypothesized that those with lower quality of life scores would have lower adherence rates and that higher nausea would predict lower adherence. Neither the child- nor caregiver-reported models supported these hypotheses.

**HRQoL (Total and Nausea) as Dependent Variables.** All continuous variables were normal, and homogeneity of variance criteria were met as relevant. Preliminary analyses examining potential covariates of total HRQoL and nausea HRQoL revealed that the combination of demographic variables correlated to each DV differed based on respondent (child versus caregiver). As such, covariates in each of the models were specific to the outcome

variable (*Table 10*). Two mixed ANOVAs were conducted to examine whether there were differences across adherence groups in longitudinal total HRQoL (child- and caregiver-reported). Two additional mixed ANOVAs were conducted to examine whether there were differences across adherence groups in longitudinal nausea HRQoL (child- and caregiver-reported).

**Relationship Between Adherence Group and Child-Reported Total HRQoL.** Within the child-reported model, only time point was significantly related to total HRQoL ($F(2, 84) = 4.53$, $p = 0.01$). Indicating that while child-reported total HRQoL for each adherence group changed significantly over time, child-reported total HRQoL did not significantly differ between the two adherence groups (*Figure 10*). Moreover, although child-reported total HRQoL was significantly correlated to baseline maternal education, number of people in the home, income, and ethnicity and race, cross-sectionally, they were not significantly related to longitudinal total HRQoL ($p > 0.05$).

**Relationship Between Adherence Group and Caregiver-Reported Total HRQoL.** Within the caregiver-reported model, baseline gender, age group, income, and maternal education were not significantly related to longitudinal HRQoL, despite significant cross-sectional correlations ($p < 0.05$). Significant differences in caregiver-reported total HRQoL were not observed between the two adherence groups (*Figure 11*). It was hypothesized that nonadherence would predict lower total quality of life; neither child- nor caregiver-model supported this hypothesis.

**Relationship Between Adherence Group and Child-Reported Nausea HRQoL.** Within the child-reported model, only timepoint was significantly related to nausea HRQoL ($F(1, 95) = 3.28$, $p = 0.04$). Indicating that while child-reported nausea HRQoL for each adherence group also changed significantly over time, child-reported nausea did not significantly differ between the two adherence groups (*Figure 12*). Although cross-sectionally related to

child-reported nausea HRQoL, baseline maternal education, study group, and race were not significantly related to longitudinal total HRQoL ($p > 0.05$).

**Relationship Between Adherence Group and Caregiver-Reported Nausea HRQoL.** Within the caregiver-reported model, baseline gender, age group, income, or maternal education were not significantly related to longitudinal nausea HRQoL, despite being cross-sectionally correlated ($p > 0.05$). Caregiver-reported nausea did not significantly differ between the two adherence groups (*Figure 13*). It was hypothesized that higher adherence would predict more nausea; neither child- nor caregiver-model supported this hypothesis.

## Discussion

Adherence during the maintenance phase of pediatric cancer treatment is critical to prevent relapse and ensure long-term, event-free survival. Comprehensive research investigating longitudinal predictors of nonadherence in pediatric cancer populations is limited. Although a number of factors have been proposed as potential barriers to adherence (Bhatia, 2011; Bhatia et al., 2012; Kondryn et al., 2011; Pritchard et al., 2006; Rohan et al., 2017; Rohan, Drotar, et al., 2015), including demographic and person-level factors (e.g., patient gender, age, ethnicity, race, youth and caregiver depressive symptoms, health beliefs and outcome expectations) and treatment factors (e.g., dose, daily adherence behaviors), these factors are not routinely investigated in research focused on patterns of medication adherence. As such, the current study aimed to expand our understanding of factors related to maintenance phase adherence by examining how additional individual and family level factors, often associated with adherence, relate to 6MP adherence during maintenance phase. These factors included, but were not limited to, number of younger children in home, pill burden, developmental phases, health beliefs, family communication patterns, and health-related quality of life.

The current study's aims were threefold: (1) describe individual, family, and medical characteristics among three medication adherence group trajectories across 15-months, (2) identify predictors of 6MP medication adherence group membership (adherent vs nonadherent), and explore potential between group differences (i.e., Latinx, non-Latinx, white) of predictors of adherence, and (3) examine an exploratory bidirectional predictive model to examine the relationship between quality of life and medication adherence group membership. Better understanding of adherence behaviors over time and factors that predict adherence during maintenance phase are critical for the development of effective and relevant person-centered resources and interventions.

**Characteristics of the three adherence group trajectories across 15-months in a cohort of pediatric cancer patients**

Results demonstrated significant differences in individual-, medical- and family-level factors across the three adherence groups (*Table 2a*; *Table 5*). As hypothesized, youth in the optimal adherence group were significantly younger (continuous age) than those in the moderate adherence group and had significantly lower daily 6MP doses than youth in the moderate adherence group across all three timepoints. Additional findings demonstrated that youth in the optimal adherence group reported higher positive outcome expectancy from taking their medication than youth in the moderate adherence group at baseline. These findings indicate that membership in the optimal adherence group was related to both individual and medical factors. Moreover, these results support past work indicating that youth's adherence behaviors are influenced by their perceptions of the effectiveness and/or necessity of their medications (Santer et al., 2014) and age (Landier, 2011).

Contrary to our hypotheses, youth in the moderate adherence group were not significantly older than youth in the chronically nonadherent group and, surprisingly, at baseline youth in the

chronically nonadherent group were prescribed lower 6MP daily doses (i.e., less pill burden) on average compared to youth in the moderately adherent group. Although dosage was lower for those in the chronically nonadherent group compared to those in the moderate adherence group, these differences did not reach significance. Given the relatively small and uneven distribution of youth in the moderately adherent versus chronic nonadherent groups, it is possible that these differences might reach significance in a larger sample. Exploratory analyses indicated that youth in the chronically nonadherent group reported less frequent general communication with their caregivers at baseline compared to youth in the optimal adherence group and were more likely to have younger children in the home compared to youth in the moderate adherence group. As such, it is possible that membership in the chronically nonadherent group was related more to family-level factors than individual or medical factors than membership in the other two groups. These findings lend support to the need to consider social determinants of health and youth's home environment when assessing and appraising health behaviors and outcomes (WHO 2016; CP Jones, 2000; Rohan & Winter 2021).

When collapsing the moderately adherent and chronically nonadherent groups into the 'nonadherent group' for analyses in Aims 2-3, age remained significantly different between the nonadherent and adherent groups, dosage differences were significant at all three timepoints, baseline positive outcome expectancy remained significantly different between the groups, and baseline differences in adherence intent across the groups emerged (*Table 2b*). While general differences between the adherent and nonadherent groups remained in the expected direction, future studies may aim to recruit larger samples so that predictive models may not need to be collapsed. This would allow further exploration into specific factors that predict membership in three (optimal vs moderately adherent vs chronically nonadherent) with variable intercepts and slopes, particularly the chronically nonadherent group whose slope (-2.8) was much larger than

the other two groups (Rohan, Drotar, et al., 2015). That said, it is notable that those in the moderately adherent and chronic nonadherent groups both never reached adherence levels of 95%, which is indicative of better prognostic factors in pediatric ALL and LBL, including decreased risk for disease relapse and mortality (Bhatia et al., 2012, 2015).

**Identifying predictors of 6MP medication adherence group (adherent versus nonadherent) in a cohort of pediatric cancer patients**

In comprehensive predictive models, examining several factors often related to mediation adherence, our findings indicated that developmental age group was the strongest predictor of 6MP adherence group (adherent versus nonadherent), even when controlling for other medical- (e.g., dose), individual- (e.g., beliefs about medication) and family-level (e.g., number of younger siblings in home, caregiver-child communication) factors; within both child-reported and caregiver-reported predictive models. Specifically, youth in the pre-adolescent and early-middle adolescent age groups were at significantly lower risk of being in the nonadherent group than youth in the middle-late adolescent age group. These findings align with past work indicating that adherence declines over adolescence (Bhatia et al., 2012; Jamison et al., 1986; Mancini et al., 2012; Partridge et al., 2002; Reed-Knight et al., 2014; Shaw et al., 2003) and that older adolescents often have unique barriers to adherence that are amplified by their unique and often challenging developmental period (Evan & Zeltzer, 2006; Gutiérrez-Colina et al., 2016; Landier, 2011).

Future work exploring adherence in this age group could be strengthened by examining other domains known to impact health behaviors in older adolescents, such as executive functioning (Evan & Zeltzer, 2006; Gutiérrez-Colina et al., 2016; Kazak & Noll, 2015), alliance with health care providers (Steinberg et al., 2020; Trevino et al., 2013), and perceived readiness for independent self-care (Goethals et al., 2020; Haarbauer-Krupa et al., 2019). Indeed, past

work examining adolescents' general attitudes towards and experience with treatment (Barbara L. Jones et al., 2010; Steinberg et al., 2020), highlights that AYA oncology patients often feel as though clinic environments are tailored more towards younger patients than older adolescents and that conversations with medical providers may be difficult to follow (e.g., use of medical jargon). Guidelines and recommendations to consider when working with AYA populations are available (Hayes-Lattin et al., 2010; Nass et al., 2015) and may serve as reference guides for additional domains to consider in future research. Moreover, the current study did not measure the quality and clarity of conversations with healthcare providers. As such, future work may benefit from standardized measures of domains of communication between adolescents and providers (e.g., treatment knowledge, perception of provider openness for questions), as it cannot be assumed that all patients begin maintenance phase with the same level of treatment understanding.

While dosage was significantly related to adherence group membership, dosage was not a stronger predictor than age group in the current model when controlling for all other factors. Exploratory findings further investigating the relationship between age group and dosage indicated that age group and dosage were significantly related, such that as age group increased dosage increased as well. These findings demonstrate that, in general, older adolescents have a higher pill burden than pre-adolescents and younger adolescents. This is likely related to older adolescents having a greater BMI due to height and weight, and thus a higher dose intensity required for continued remission. Currently, 6MP is only available in 50 mg doses, which increases risk for pill burden especially for adolescents who are already at a vulnerable developmental period and at risk of nonadherence due to competing demands. Efforts to advocate for 6MP to be available in various forms (50mg, 75mg, 100mg), at the pharmaceutical and insurance levels, may be considered as this could help to ameliorate the pill burden older

adolescents face. Additionally, age group analyses indicated that youth in the middle-late adolescence group reported significantly higher expectations of negative outcomes from taking their medication at baseline than youth in the early-middle adolescence group. These findings suggest that education related to medication should be tailored across the developmental trajectory, especially as children transition to adolescence, and adolescents to young adulthood, to meet the patients' unique developmental needs and concerns. For example, research indicates that fertility issues often arise as an important topic for older adolescent cancer patients (Evan & Zeltzer, 2006; Sisk et al., 2019). As such, developmentally appropriate information regarding how 6MP affects fertility could be important to share with older adolescents, as this may be a salient potential negative outcome among this age group.

The complex treatment regimen and increased treatment burden for pediatric cancer patients often poses significant challenges for children, adolescents, and their families. Past work has demonstrated that increased treatment burden has been related to increased rates of nonadherence (Pritchard et al., 2006; Ruddy et al., 2009). Previous research also suggests that a patient's health beliefs (i.e., how they view their illness and associated treatment) likely directly influences their medication adherence (Buchanan et al., 2014; Pritchard et al., 2006). Prior research has proposed that patients who perceive their illness as serious, perceive themselves as vulnerable, and recognize that treatment will be effective in curing their illness are likely to have higher rates of medication adherence (Jamison et al., 1986; Malbasa et al., 2007; Santer et al., 2014). Similar to this past work, our results indicated that higher positive outcome expectancies increased the likelihood of membership in the adherent group (in the caregiver model). Interestingly adherence intent nor negative outcome expectancy were significantly predictive of adherence in the current study. These findings indicate the need and value of education related to the positive benefits of taking 6MP medication as prescribed. Indeed, focus groups with

caregivers of children with cancer revealed that even caregivers often wish for more information regarding treatment timeline, overviews, and possible side effects (Ringnér et al., 2011). Prioritizing informational sessions related to treatment and the benefits and risks of medication might help to positively enhance youth's health beliefs.

Contrary to hypotheses, child- and caregiver-reported depression did not significantly relate to adherence group membership. Given the restricted range and variability of both caregiver- and child-reported depressions scores across time in the current cohort it is possible that the CDI and BDI were not clinically sensitive enough to evaluate the unique psychological experiences of the youth and caregivers in the current sample. It is also possible that youth and their caregivers who were included in the present sample had minimal psychological distress and thus lower rates of depressive symptoms comparative to previous work. Although past work, including youth with cancer, demonstrated that the CDI can be used in chronically ill populations with good overall reliability (Saoji et al., 2019), reliability statistics for the CDI in this sample were low. Due to possible health-related activity restrictions during the maintenance phase of treatment, semi-structured interviews or open-ended depression measures could be useful in pediatric cancer populations to differentiate between what youth can and cannot do due to their treatment/diagnosis and what youth are experiencing due to mood or emotion concerns.

Contrary to hypotheses, caregiver- and child-reported total communication frequency did not significantly relate to adherence group membership when controlling for other variables of interest. The Parent-Adolescent Conflict Scale (PAC) questionnaire used in the current study measured general communication frequency and intensity of conversations related to 15 specific issues generally discussed during adolescence. While this general communication assessment provides information regarding how often caregivers and children discuss general topics (e.g., chores, homework, hanging out with friends) and how intense these conversations typically

were, it is possible that simply discussing topics may not be as impactful on health behaviors, such as adherence, as other caregiver-child dynamics. Guided by systems theory (Bronfenbrenner, 1979; I. M. Miller et al., 2000) and past work in other pediatric chronic illness populations (Fredericks et al., 2007; Killian et al., 2018), caregiver-child cohesion and family functioning are two constructs that should be explored in future work as they might shed light on important family processes that may be related to medication adherence. It is possible that the quality of conversations and how understood both parties feel may be more important than the mere occurrence of conversations. Incorporating measures such as the Family Assessment Device (Epstein et al., 1983) and the Family Adaptability and Cohesion Scales (FACES III, Olson, 1986), which is available in Spanish (Flores & Sprenkle, 1989) and has been normed for Latinx families (Baer & Schmitz, 2007), could strengthen future work. Among Latinx families, family cohesion is known to be related to acculturation (Baer & Schmitz, 2007). As such, acculturation and/or biculturalism should also be assessed when examining the relationship between family cohesion and adherence behaviors among Latinx patients.

Contrary to hypotheses, number of younger children in the home was not significantly related to adherence group membership. While various family-level factors were evaluated in this study (e.g., number of younger children/siblings in the home, caregiver- and child- reported communication frequency and intensity), these measures do not fully capture dynamic family processes, particularly within the context of pediatric chronic illness management. For example, although number of siblings in the home has been significantly related to adherence in past work (Tebbi et al., 1986), conceptually number of younger children/siblings in the home was considered a proxy measure for competing demands in the household due to other children in the home. However, a static number of younger children in the home does not directly capture caregiver demands or shed light on other factors that may cause differences across families with

the same number of children in their homes. For example, number of siblings does not account for variable sibling needs (e.g., developmental delays, family expectations, chronic health conditions) or caregiver-perceived difficulties related to medication adherence in the context of their unique home and family (e.g., balancing the needs of all children in the home, difficulties establishing medication routine). The Parent Medication Barriers Scale (Simons & Blount, 2007) has been used in past work investigating barriers to medication adherence among patients with inflammatory bowel disease (Reed-Knight et al., 2013) and solid organ transplantation (Danziger-Isakov et al., 2016); however, this measure assesses perceived barriers related to adolescents taking their medication (e.g., too many pills, does not like the taste, does not want friends to see), not perceived barriers for caregiver involvement in medication management or assessment of a family routine around medication management. As such, future work is encouraged to assess caregiver/family-specific and caregiver-perceived barriers to involvement or family-specific reasons for noninvolvement in medication management to better understand caregiver involvement and how it relates to maintenance phase medication management.

In the predictive models included in Aim 2a, caregiver- and child-reported variables were evaluated in separate models to account for shared variance and multicollinearity. In the majority of predictive models, the QICu value did not differ substantially when using child versus caregiver report, with the exception of total communication frequency. Future work might benefit from analyzing report congruency and discrepancy (De Los Reyes et al., 2019), as differences in caregiver- and child-reported accounts (across domains) can provide information surrounding the caregiver-child relationship. Given past work demonstrating that caregiver-child discrepancies on parental monitoring assessment was able to predict child delinquent behaviors 2 years later in ways that individual reports could not (De Los Reyes et al., 2010), examining

discrepancies in reports of caregiver monitoring or involvement in medication management could shed light on important dynamics that affect adherence.

**Identify possible between group differences of predictors of 6MP medication adherence patterns**

Preliminary exploratory analyses indicated possible between group differences (i.e., Latinx, non-Latinx white) of predictors of 6MP adherence patterns. Bonferroni corrections indicated that some cross-sectional relationships did not remain significant based on the corrected value of $p = 0.006$. Given that corrections are utilized when analyses do not have directional hypotheses, specific research questions, or when less robust statistical analyses are utilized (R. A. Armstrong, 2014), it is recommended that future work prioritize recruiting large and diverse samples to allow for more robust analyses or identifying possible ethnicity-specific predictor to allow for apriori hypotheses.

Within the Latinx subsample, single factor models indicated that longitudinal 6MP dosage and baseline positive outcome expectancy significantly predicted adherence group membership. Specifically, among Latinx youth as dose increased so did risk for nonadherence and, conversely, as POE increased risk for nonadherence decreased. Conversely, within the white subsample, single factor models indicated that baseline age group, baseline and longitudinal 6MP dose, and longitudinal child-reported and caregiver-reported communication frequency significantly predicted adherence group membership. Specifically, as age group and 6MP dose increased risk of nonadherence increased and, conversely, more frequent communication (child- and caregiver- reported) was associated with decreased risk of nonadherence. These findings should be interpreted with caution as single factor models are limited as they do not account for possible confounding factors. Nevertheless, these findings revealed interesting information about cross-sectional versus longitudinal analyses and highlight the importance of assessing both cross-

sectional data and patterns of data when possible. Moreover, these findings highlight the potential importance of health beliefs in Latinx patients' health behaviors (Leininger, 1997).

Additionally, the relationship between ethnicity and adherence should be interpreted cautiously as these analyses centralize outcomes without consideration of processes and social stratification (García et al., 1996). Latinx pediatric cancer patients' experiences with cancer treatment and health behaviors may be significantly influenced by cultural factors, such as acculturation and values (Gray et al., 2014; Munet-Vilaró, 2004). A main cultural factor that has been explored to date is acculturation. Acculturation is defined as a process by which contact with a different culture results in the modification of the culture of a group or individual (Redfield et al., 1936). Acculturation orientations have been conceptualized in two domains: the adoption of mainstream culture and/or the maintenance of one's own ethnic-origin culture, with various possible combinations that may be related to differing degrees of acculturative stress (i.e., assimilation, integration; Berry, 2005). Literature supports a bidirectional model of acculturation and has demonstrated its advantages over focusing on unidimensional models to predict outcomes, given that individuals can hold multiple cultural orientations (Nguyen & Benet-Martínez, 2007). As such, recent literature has shifted towards assessing the dynamic process of cultural adaptation referred to as biculturalism (i.e., the degree to which individuals have internalized aspects of mainstream and ethnic culture) rather than linear measures of acculturation. Recent findings indicate that acculturative family distancing is associated with decreases in family cohesion among US-Born youth and their parents (Nair, Roche, & White, 2018). Thus, including measures of biculturalism, acculturative family distancing, and values in future work with Latinx patients could provide more information about the nuanced ways that the dynamic processes of culture relate to health behaviors and outcomes.

**Examining a bidirectional predictive relationship between quality of life and adherence**

Given past research demonstrating a potentially bidirectional relationship between adherence and HRQoL within samples of children with chronic illnesses (Fredericks et al., 2008; Hommel et al., 2009; Rapoff, 2010), exploratory analyses examined a potential bidirectional predictive relationship between quality of life and adherence. In this cohort of pediatric oncology patients, surprisingly, results indicated that longitudinal quality of life (total and nausea) and adherence trajectories were not significantly related in either direction (e.g., quality of life predicting adherence, adherence predicting quality of life). Past work focused on populations with significantly greater pill burden (e.g., Crohn's 12-18 pills a day; Hommel et al., 2009) and lifetime chronic illness (e.g., sickle cell, asthma; (Barakat et al., 2005; Fiese et al., 2005). As such, it is possible that although disease self-management is taxing on patients and families, adherence and quality of life may not affect each other as much during the maintenance phase of cancer treatment as in other chronically ill populations. This may be related to having decreased illness burden during maintenance relative to other phases. In maintenance, patients can often return to some of the activities they did prior to cancer treatment and have fewer medical visits.

Furthermore, it is important to note that the PedsQL 3.0 Cancer Module had low Cronbach alpha statistics among Latinx patients who completed the 5-7 year old interview version (*Table 3*). Given the low alpha statistics, all youth who completed the 5-7 year old version were excluded from statistical analyses in Aim 3. These low alpha values align with findings from past work utilizing the generic PedsQL among an Argentinian sample ($\alpha$ range = 0.28–0.76; Roizen et al., 2008). As such, it is possible that this measure may not be a good fit for Latinx children and their families. It is possible that construct equivalence may not have translated sufficiently in this version. For example, the item "Does your medicine make you sick to your stomach?" was translated directly to "*Te hacen sentirte mal del estómago tus medicinas*?" rather than "*Tus medicinas te dan un dolor de estómago*?/Does your medicine make

your stomach hurt?" which may have been more culturally and developmentally appropriate for youth in that age group. Future work should consider other measures of HRQoL for younger (5-7) Latinx children and their families.

**Limitations and Future Directions**

While the current study provides important information regarding specific individual, family, and medical factors that may relate to and predict 6MP adherence during the maintenance phase of treatment, it is important to note limitations of the current study. The demographic characteristics of the patients enrolled at each site reflected the general population in the areas where each hospital was located. Consequently, the generalizability of current findings is limited to Latinx (predominantly Mexican) and non-Latinx, white patients receiving maintenance treatment in the geographic regions included in our study. Future multi-site studies, should be intentional about including hospitals known to serve Black, Asian, and Indigenous communities, as these populations are often excluded from pediatric cancer research (Aristizabal et al., 2015; Chen et al., 2014; Sateren et al., 2002; Underwood, 2000).

Additionally, the generalizability of findings related to Latinx patients' adherence behaviors are limited, first, due to study location. Los Angeles and Dallas have strong and historically established Latinx communities and many institutional supports and resources for Latinx families (Cobb et al., 2020; Potochnick et al., 2012). Emerging Latinx communities have distinct needs and barriers (Brietzke & Perreira, 2017; Huq et al., 2016), such as a lack of bilingual resources (Corona et al., 2009; Wells et al., 2008) and increased concerns of discrimination (Potochnick et al., 2012). Furthermore, in more established communities, later generation immigrants with greater English proficiency and insights into navigating barriers may serve as supports (Duong et al., 2016). Consequently, Latinx patients in emerging Latinx communities may have markedly different experiences, outcomes, and needs than those in

established Latinx communities. As such, there is a need for future studies to examine adherence and factors related to adherence among youth from emerging Latinx communities. Second, recruitment of Latinx patients and families from other regions and countries of origin would also help to expand our understanding of adherence across a variety of Latinx communities. Third, although relatively large compared to past work, the size of the Latinx sample in the current study ($n$ = 47, 34%) limited the statistical approaches appropriate for our data. Due to power restrictions, analyses evaluating predictors of 6MP adherence membership among Latinx patients were limited to one predictor at a time. Thus, it was not possible to assess potential covariates in our between group (i.e., Latinx; non-Latinx, white) data analyses. Future work should aim to include a greater number of Latinx patients. This would allow for more powerful statistical analyses and the ability to examine intersectional identities known to influence family expectations among Latinx families (e.g., gender socialization; Raffaelli & Ontai, 2004).

Another important limitation relates to the lack of variables measuring child, caregiver, and family experiences with racism (individual, institutional/structural). This is particularly notable given the various ethnic and racial groups included in our sample (12% non-Latinx racially minoritized (e.g., Black, Asian), 34% Latinx). For decades, researchers have elucidated that racism operates at multiple levels, ranging from internalized to institutionalized (C. P. Jones, 2000; Ture & Hamilton, 1992). The American Academy of Pediatrics has recognized racism as a core social determinant of health that drives many of the inequities experienced by children and adolescents (Trent et al., 2019). The World Health Organization (2016) defines social determinants of health as "the conditions in which people are born, grow, live, work and age." These determinants are influenced by factors such as the distribution of money, power, and resources at global, national, and local levels and have been linked to inequities. Moreover, these inequities are caused by economic, political, and social conditions (including racism) and not

individual choices or genetic predisposition (World Health Organization, 2016). Indeed, institutional racism is known to manifest itself in both 'material conditions' (e.g., access to quality education, neighborhoods, medical facilities) and 'power' (e.g., access to information, resources, and voice; C. P. Jones, 2000), which are often outside of an individuals' control.

While there is no standard measure for structural racism, past work has relied on various indices (e.g., redlining, mortgage lending), socioeconomic status data (e.g., employment rate proportions), and self-report measures (e.g., perceived racism) to investigate the relationship between structural racism and outcomes (Groos et al., 2018). Studies utilizing these measures have demonstrated that structural racism impacts a range of health behaviors and outcomes in adults, including colorectal cancer survivorship (Kacanek et al., 2019), hypertension treatment adherence (Greer et al., 2014), and delayed HIV testing (Scott et al 2014). Although past work has demonstrated the relationship between structural racism and child mental health and school outcomes (S. C. T. Jones & Neblett Jr., 2019; Mougianis et al., 2020; Owens, 2020), research investigating the relationship between racism and child physical health outcomes and behaviors is scarce (Pachter & Coll, 2009) and available measures are limited (e.g., forms of racism assessed, only one racial/ethnic group; Braddock et al., 2021). Nevertheless, measures such as the Perception of Racism in Children and Youth measure (PRaCY; Pachter, Szalacha, et al., 2010) have demonstrated promise among pediatric patients with sickle cell disease (E. O. Wakefield et al., 2018). Future work could benefit from assessing children's experiences with racism (individual and institutional) as a means to better understand processes and mechanisms of inequities (García et al., 1996); particularly with measures designed using qualitative, mixed, and community-based methodologies (S. C. T. Jones & Neblett, 2017). Recent work by Isaac and colleagues (2020) provides guidance on several additional biopsychosocial factors and social

determinants of health that warrant inclusion in future pediatric cancer treatment adherence studies.

## Conclusion

The current study substantially adds to the literature base as it expands our understanding of factors related to youth's adherence to 6MP medication during maintenance phase treatment of ALL and LBL. Findings indicate that adolescent developmental phase was the strongest predictor of 15-month adherence group membership. Better understanding of potential individual and family level factors that might impact this relationship is critical so that we may develop resources and interventions for these youth who are at increased risk for nonadherence, and consequently relapse. Dosage and health beliefs, specifically positive outcome expectancy, also significantly predicted adherence group membership. These findings demonstrate the continued need to provide person-centered tailored interventions to patients, while considering individual level characteristics. Exploratory analyses indicated the possibility of between group (i.e., Latinx; non-Latinx white) differences with respect to predictors of 6MP adherence. Additional multi-site studies are needed to further explore possible between group differences of predictors of adherence, as well as examine possible ethnicity-specific predictors of adherence such as cultural values (e.g., familismo, respeto), spiritualism, biculturalism. This future work may incorporate measures of cultural values, expectations, and processes to better understand the underlying drivers for these possible unique predictors. While the current study adds considerably to our understanding of adherence during maintenance phase, additional work in this area focused on preventive and therapeutic interventions remains critical to increase positive outcomes for a vulnerable cohort of patients; and, to ultimately reduce morbidity and mortality related to medication nonadherence.

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Table 1. Summary of Data Analyses, Research Aims, Hypotheses, and Purpose of Data Analyses for Aims 1-3.

| Aims | Hypotheses | Data Analytic Method | Purpose of Analysis |
|---|---|---|---|
| 1. Describe characteristics for each of the three adherence group trajectories across 15-months in a cohort of pediatric cancer patients | • Children in the moderate adherence group will be older than children in the optimal adherence and chronic nonadherence groups.<br>• Dosage will range across the groups, with children in optimal adherence group (lowest dose), moderate adherence group (second lowest dose), and chronic nonadherence (highest dose) | • Descriptive Statistics | • Describe individual- and family-level factors across 15-months for each of the three group-based trajectories |
| Preliminary Analyses for Aims 2-3 | • N/A | • Correlations (continuous factors)<br>• Chi-Square (categorical factors) | • Identify covariates to include in Aims 2-3 analyses |
| 2a. Identify predictors of 6MP medication adherence group (adherent versus nonadherent) in a cohort of pediatric cancer patients | • Higher levels of caregiver and patient depression, greater number of younger siblings/children in the home, greater levels of caregiver-child conflict, and higher beliefs of negative outcomes from taking medication will predict membership in the nonadherent group.<br>• More frequent communication, greater adherence intent, and higher beliefs of positive outcomes from taking medication will predict membership in the adherent group. | • Generalized linear mixed effects models (mixed effects longitudinal logistic regression) | • Identify which individual- and family-level factors predict adherence group membership |
| 2b. Exploratory Analyses: Identify possible between group differences of predictors of 6MP medication adherence patterns | • Predictors of adherence might differ between non-Latinx patients and Latinx patients. | • Descriptive statistics<br>• Correlations and chi-squares<br>• Binominal logistic regression | • Determine whether the individual- and family-level factors that predict adherence vary between Latinx and non-Latinx white children |
| 3. Exploratory Analysis: Examine bidirectional predictive relationship between quality of life and adherence | • Nonadherence will predict lower total quality of life scores<br>• Those with lower quality of life scores will have lower adherence rates<br>• Higher nausea will predict lower adherence | • General linear mixed models for normal/continuous outcomes<br>• Generalized linear mixed effects models for non-normal/categorical outcomes (mixed effects longitudinal logistic regression) | • Examine bidirectional model of adherence group predicting quality of life and quality of life predicting adherence group |

**Abbreviations.** N/A, not applicable; 6MP, 6-mercaptopurine

Table 2a. Demographic and Medical Characteristics of Baseline Sample and Trajectory Groups (3 group)

| | Full Sample (*N* = 139) | Optimal Adherence Group (*n* =88) | Moderate Adherence Group (*n* = 26) | Chronically Non-adherent Group (*n* = 17) |
|---|---|---|---|---|
| Mean Patient Age, M (SD) | 12.29 (±3.4) | 11.75 (3.38)[a] | 13.57 (3.36) | 13.34 (3.4) |
| Patient Age Group, n (%) | | | | |
| Pre-adolescence (7-9.99) | 50 (36) | 38 (43) | 5 (19) | 3 (18) |
| Early-Middle adolescence (10-14.99) | 48 (35) | 30 (34) | 10 (39) | 7 (41) |
| Middle-Late adolescence (15-19) | 41 (29) | 20 (23) | 11 (42) | 7 (41) |
| Type of Cancer Diagnosis, n (%) | | | | |
| ALL | 133 (96) | 16 (13) | 25 (20) | 85 (67) |
| LBL | 6 (4) | 1 (20) | 1 (20) | 3 (60) |
| Patient Gender, n (%) | | | | |
| Female | 45 (32) | 28 (32) | 8 (31) | 7 (41) |
| Male | 94 (68) | 60 (68) | 18 (69) | 10 (59) |
| Patient Education, n (%) | | | | |
| Elementary (including 6th) | 77 (55) | 55 (63) | 10 (38) | 8 (47) |
| Middle School | 26 (19) | 16 (18) | 6 (23) | 2 (12) |
| High School | 36 (26) | 17 (19) | 10 (39) | 7 (46) |
| Patient Ethnicity, n (%) | | | | |
| Latinx | 47 (34) | 31 (35) | 9 (35) | 5 (29) |
| Non-Latinx, Racially Minoritized | 16 (12) | 10 (11) | 3 (12) | 2 (12) |
| Non-Latinx, white | 76 (55) | 47 (53) | 14 (53) | 10 (59) |
| Number of Kids in Home, n (%) | | | | |
| 1 (patient only) | 19 (14) | 11 (13) | 5 (19) | 1 (6) |
| 2 kids | 52 (37) | 32 (36) | 11 (42) | 7 (41) |
| 3 kids | 47 (34) | 32 (36) | 6 (23) | 7 (41) |
| 4+ kids | 21 (15) | 13 (15) | 4 (15) | 2 (12) |
| Breakdown of Kids in Home, n (%) | | | | |
| Younger kids in home (y/n) | 78 (56) | 54 (61) | 9 (35) | 13 (81)[b] |
| Older kids in home (y/n) | 73 (53) | 46 (52) | 16 (61) | 8 (47) |
| Caregiver Gender, n (%) | | | | |
| Female-identifying caregiver | 128 (92) | 84 (96) | 23 (88) | 14 (82) |
| Male-identifying caregiver | 11 (8) | 4 (4) | 3 (12) | 3 (18) |
| Primary Caregiver's Marital Status, n (%) | | | | |
| Married | 96 (69) | 61 (69) | 15 (58) | 13 (76) |
| Not Married | 43 (31) | 27 (31) | 11 (42) | 4 (24) |
| Household Income[c], n (%) | | | | |
| < $18,745 | 36 (26) | 23 (27) | 10 (38) | 1 (6) |
| $18,745 - $32,874 | 18 (13) | 10 (12) | 5 (19) | 3 (19) |
| $32,875 - $48,999 | 13 (9) | 6 (7) | 1 (4) | 5 (31) |
| $49,000 - $72,999 | 20 (14) | 15 (18) | 3 (12) | 1 (6) |
| $73,000 - $126, 500 | 31 (22) | 20 (23) | 6 (23) | 3 (19) |
| > $126,500 | 17 (12) | 11 (13) | 1 (4) | 3 (19) |
| Household Composition, n (%) | | | | |
| One caregiver household | 45 (32) | 25 (28) | 13 (50) | 6 (35) |
| Two caregiver household | 94 (68) | 63 (72) | 13 (50) | 11 (65) |

**Abbreviations.** M, mean; SD, standard deviation.

[a] F (2, 130) = 3.83, p = 0.024; Tukey post-hoc analyses. Adolescents in the optimal adherence group were significantly younger than those in the moderate adherence group, $M_{diff}$= 1.83 years, p = 0.044.

[b] $x^2(1, 130) = 9.815$, p = 0.007; chronically non-adherent patients were more likely to have younger children in home.

[c] Four families did not report on income. Full sample for income (n = 135), across the groups (n = 127).

Table 2b. Baseline Demographic and Medical Characteristics of Adherent and Non-Adherent Trajectory Groups

| | Full sample (*N* = 131) | | Latinx sample (*n* = 45) | | non-Latinx, white (*n* = 71) | |
|---|---|---|---|---|---|---|
| | Nonadherent Group (*n* = 43) | Adherent Group (*n* = 88) | Nonadherent Group (*n* = 14) | Adherent Group (*n* = 31) | Nonadherent Group (*n* = 24) | Adherent Group (*n* = 47) |
| Patient Age Group, n (%) | | | | | | |
| Pre-adolescence (7-9.99) | 8 (19) | 38 (43)[a] | 2 (14) | 11 (36) | 5 (21) | 24 (51)[b] |
| Early-Middle adolescence (10-14.99) | 17 (40) | 30 (34) | 6 (43) | 10 (32) | 9 (37) | 14 (30) |
| Middle-Late adolescence (15-19) | 18 (41) | 20 (23) | 6 (43) | 10 (32) | 10 (42) | 9 (19) |
| Number of Young Children in Home, M (SD) | 0.8 (1.0) | 1.0 (1.0) | 1.2 (1.1) | 1.5 (1.1) | 0.6 (0.8) | 0.7 (0.9) |
| Study Group | | | | | | |
| Intervention, n (%) | 19 (44) | 48 (55) | 7 (50) | 14 (45) | 8 (33) | 26 (55) |
| Control, n (%) | 24 (56) | 40 (45) | 7 (50) | 17 (55) | 16 (67) | 21 (45) |
| Diagnosis duration (years), M (SD) | 1.3 (0.3) | 1.3 (0.4) | 1.4 (0.3) | 1.3 (0.3) | 1.2 (0.4) | 1.3 (0.4) |
| Dose (mg) baseline, M (SD) | 102.8 (44.1) | 77.7 (36.5)** | 121.4 (55.3) | 87.9 (40.8)* | 93.5 (34.8) | 72.3 (30.9)* |
| Dose (mg) 6mo, M (SD) | 107.0 (50.9) | 88.4 (37.1)* | 126.9 (70.3) | 94.4 (39.1) | 93.1 (37.4) | 84.2 (34.8) |
| Dose (mg) 15mo, M (SD) | 125.8 (47) | 91.7 (40.9)** | 144.4 (57.0) | 98.5 (40.2)* | 106.9 (34.1) | 83.8 (41.8)* |
| NOE (baseline), M (SD) | 33.0 (12.9) | 32.2 (13.4) | 34.6 (14.7) | 35.1 (15.7) | 32.1 (12.6) | 30.1 (11.8) |
| NOE (6mo), M (SD) | 30.8 (13.1) | 30.2 (13.7) | 36.1 (14.2) | 33.0 (14.4) | 27.4 (11.5) | 27.9 (13.9) |
| NOE (15mo), M (SD) | 32.3 (13.8) | 31.2 (14.9) | 40.0 (15.7) | 34.2 (15.7) | 27.6 (11.3) | 29.6 (15.5) |
| PT (baseline), M (SD) | 45.7 (13.7) | 46.4 (12.8) | 49.8 (14.5) | 49.4 (12.2) | 44.0 (13.7) | 44.3 (12.0) |
| PT (6mo), M (SD) | 44.2 (14.4) | 42.9 (13.8) | 49.3 (14.5) | 47.4 (13.7) | 41.1 (13.8) | 40.4 (13.2) |
| PT (15mo), M (SD) | 43.4 (13.5) | 42.8 (13.6) | 50.2 (14.8) | 48.3 (14.5) | 40.1 (12.4) | 40.2 (12.5) |
| POE (baseline), M (SD) | 112.4 (15.5) | 118.3 (13.3)* | 109.5 (14.3) | 118.6 (10.8)* | 117.1 (12.4) | 118.7 (15.4) |
| POE (6mo), M (SD) | 113.2 (19.7) | 117.1 (14.8) | 111.2 (15.7) | 111.9 (16.6) | 116.9 (20.3) | 120.1 (12.9) |
| POE (15mo), M (SD) | 115.1 (16.1) | 118.1 (14.6) | 112.9 (15.4) | 116.0 (15.8) | 118.8 (14.3) | 118.3 (15.2) |
| Intent (baseline), M (SD) | 42.7 (5.7) | 45.0 (4.5)* | 41.4 (5.5) | 44.6 (5.4) | 44.5 (4.6) | 45.6 (3.8) |
| Intent (6mo), M (SD) | 44.2 (5.7) | 44.7 (5.2) | 42.9 (7.0) | 43.3 (6.5) | 45.1 (4.8) | 45.9 (3.4) |
| Intent (15mo), M (SD) | 43.8 (5.5) | 44.8 (5.0) | 41.5 (6.1) | 44.0 (6.2) | 45.3 (3.6) | 45.7 (3.7) |
| PAC Frequency (baseline) | 12.8 (9.9) | 14.5 (10.1) | 13.2 (5.7) | 16.4 (9.9) | 13.7 (12.2) | 13.5 (10.7) |
| PAC Frequency (6mo) | 11.5 (10.7) | 13.7 (9.2) | 16.0 (14.6) | 13.9 (7.5) | 10.5 (8.3) | 13.4 (10.6) |
| PAC Frequency (15mo) | 9.1 (8.3) | 13.8 (10.8)* | 13.3 (11.2) | 15.6 (12.6) | 7.7 (6.0) | 13.3 (10.5)* |
| PAC-P Frequency (baseline) | 13.4 (9.7) | 17.1 (12.9) | 20.2 (14.5) | 21.2 (12.9) | 10.5 (5.4) | 14.9 (13.1) |
| PAC-P Frequency (6mo) | 12.0 (11.9) | 17.1 (13.1)* | 20.6 (18.4) | 23.1 (14.5) | 8.3 (7.5) | 14.1 (11.6)* |
| PAC-P Frequency (15mo) | 13.0 (12.7) | 15.3 (12.1) | 24.3 (16.8) | 18.5 (11.7) | 7.1 (4.7) | 15.1 (13.0)*** |

**Abbreviations.** n, number; %, percentage; M, mean; SD, standard deviation; mg, miligrams; mo, months; PAC, Parent-Adolescent Communication; PAC-P, Parent-Adolescent Communication – Parent Report. **Notes.** * Significant at the 0.05 level (2-tailed); ** Significant at the 0.01 level (2-tailed); *** Significant at Bonferroni corrected 0.006 level (2-tailed).

[a] $\chi^2$ (2, 131) = 8.85, $p$ = 0.012

[b] $\chi^2$ (2, 71) = 6.86, $p$ = 0.03

Table 3. Cronbach's Alpha for Study Measures

| | Full sample | | | Latinx | | | Non-Latinx, white | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 6 month | 15 month | Baseline | 6 month | 15 month | Baseline | 6 month | 15 month |
| BAMS (Young Child) | 0.78 | 0.77 | 0.79 | 0.67[A] | 0.82 | 0.84 | 0.70 | 0.74 | 0.77 |
| BAMS | 0.73 | 0.84 | 0.79 | 0.74 | 0.84 | 0.81 | 0.70 | 0.87 | 0.82 |
| CDI | 0.66[B] | 0.66[C] | 0.72 | 0.72 | 0.60[D] | 0.72 | 0.58[E] | 0.69[F] | 0.75 |
| BDI | 0.91 | 0.92 | 0.93 | 0.93 | 0.94 | 0.93 | 0.88 | 0.90 | 0.92 |
| PAC Frequency Total | 0.82 | 0.79 | 0.82 | 0.70 | 0.79 | 0.86 | 0.85 | 0.76 | 0.80 |
| PAC-P Frequency Total | 0.88 | 0.90 | 0.88 | 0.87 | 0.92 | 0.90 | 0.87 | 0.86 | 0.87 |
| PedsQL (Young Child) | 0.89 | 0.89 | -[b] | 0.73 | (error)[a] | -[b] | 0.91 | 0.93 | -[b] |
| PedsQL (Child) | 0.87 | 0.89 | 0.88 | 0.89 | 0.86 | 0.76 | 0.85 | 0.90 | 0.91 |
| PedsQL (Adolescent) | 0.89 | 0.89 | 0.89 | 0.93 | 0.90 | 0.90 | 0.81 | 0.88 | 0.81 |
| Parent PedsQL (Young Child) | 0.84 | 0.51[G] | -[b] | 0.52[H] | (error)[a] | -[b] | 0.89 | 0.72 | -[b] |
| Parent PedsQL (Child) | 0.89 | 0.87 | 0.91 | 0.90 | 0.87 | 0.85 | 0.90 | 0.88 | 0.93 |
| Parent PedsQL (Adolescent) | 0.93 | 0.92 | 0.95 | 0.95 | 0.95 | 0.97 | 0.88 | 0.89 | 0.88 |

**Abbreviations**. BAMS, Beliefs about Medication Scale; CDI, Children's Depression Inventory; BDI, Beck Depression Inventory; PAC, Parent-Adolescent Communication; PAC-P, Parent-Adolescent Communication – Parent; PedsQL, Pediatric Quality of Life measure.

[a] Cronbach's alpha value indicated negative average covariance. This violates reliability model assumptions.

[b] All youth who were 7 years old at baseline aged up to the next form by the 15 month data collection ($n$ = 0).

Table 4. Group-Based Trajectory Modeling: Weekly Adherence (*N* = 131)

| Adherence Group Trajectory | **Parameter** | **Estimate (Std. Err.)** | **t** | **p** |
|---|---|---|---|---|
| Optimal Adherence | Intercept | 96.32 (0.83) | 115.67 | < .001 |
| | Time | -0.10 (0.06) | -1.67 | 0.09 |
| Moderate Adherence | Intercept | 67.58 (1.59) | 42.61 | < .001 |
| | Time | -0.006 (0.002) | -3.14 | < .001 |
| Chronic Nonadherence | Intercept | 62.69 (1.93) | 32.50 | < .001 |
| | Time | -2.82 (0.15) | -18.67 | < .001 |

Table 5. Medical, Individual- and Family- Level Factors Across Adherence Groups ($N$ = 131)

| | Optimal Adherence Group ($n$ =88) | Moderate Adherence Group ($n$ = 26) | Chronically Non-adherent Group ($n$ = 17) |
|---|---|---|---|
| Dose (mg) baseline, M (SD) | 77.7 (36.5)[a] | 114.2 (44.9)[a] | 85.3 (3.6)[b] |
| Dose (mg) 6mo, M (SD) | 88.4 (37.1)[a] | 118.4 (55.1)[a] | 89 (38.7) |
| Dose (mg) 15mo, M (SD) | 91.7 (40.9)[a] | 136.1 (47.1)[a] | 111.5 (45.2) |
| CDI raw (baseline), M (SD) | 1.3 (1.5) | 2.0 (2.6) | 1.1 (2.4) |
| CDI raw (6mo), M (SD) | 1.4 (1.6) | 1.7 (2.0) | 0.9 (2.0) |
| CDI raw (15mo), M (SD) | 1.3 (1.9) | 1.4 (1.8) | 0.9 (2.4) |
| Clinically Significant BDI (baseline), n (%) | 6 (46.2) | 5 (38.5) | 2 (15.4) |
| Clinically Significant BDI (6mo), n (%) | 10 (66.7) | 3 (20.0) | 2 (13.3) |
| Clinically Significant BDI (15mo), n (%) | 8 (61.5) | 4 (30.8) | 1 (7.7) |
| NOE (baseline), M (SD) | 32.2 (13.4) | 36.2 (12.9) | 28.1 (11.5) |
| NOE (6mo), M (SD) | 30.2 (13.7) | 32.7 (13.3) | 28 (12.6) |
| NOE (15mo), M (SD) | 31.2 (14.9) | 33.2 (14.5) | 31.1 (13.3) |
| PT (baseline), M (SD) | 46.4 (12.8) | 48.5 (12.6) | 41.5 (14.5) |
| PT (6mo), M (SD) | 42.9 (13.8) | 46 (14.3) | 41.5 (14.5) |
| PT (15mo), M (SD) | 42.8 (13.6) | 43.1 (12) | 43.8 (15.9) |
| POE (baseline), M (SD) | 118.3 (13.3)[c] | 110.3 (15.2)[c] | 115.6 (15.9) |
| POE (6mo), M (SD) | 117.1 (14.8) | 113.9 (15.5) | 112.1 (25.1) |
| POE (15mo), M (SD) | 118.1 (14.6) | 113.1 (14.5) | 117.7 (18.2) |
| Intent (baseline), M (SD) | 45 (4.5) | 42.9 (5.6) | 42.6 (6.1) |
| Intent (6mo), M (SD) | 44.7 (5.2) | 43.5 (5.6) | 45.2 (5.7) |
| Intent (15mo), M (SD) | 44.8 (5) | 43.1 (5.4) | 44.8 (5.7) |
| PAC Frequency (baseline) | 14.5 (10.1) | 13.0 (11.4) | 12.5 (7.5) |
| PAC Frequency (6mo) | 13.7 (9.2) | 13.1 (12.4) | 9.2 (7.5) |
| PAC Frequency (15mo) | 13.8 (10.8)[d] | 11.2 (9.6) | 6.1 (4.8)[d] |
| PAC-P Frequency (baseline) | 17.1 (12.9) | 13.1 (11.5) | 13.8 (5.8) |
| PAC-P Frequency (6mo) | 17.1 (13.1) | 13.9 (14.4) | 9.3 (6.6) |
| PAC-P Frequency (15mo) | 15.3 (12.1) | 13.5 (14.3) | 12.4 (10.6) |
| PAC Mean Conflict (baseline) | 1.4 (0.6) | 1.5 (0.6) | 1.5 (0.6) |
| PAC Mean Conflict (6mo) | 1.5 (0.5) | 1.6 (0.7) | 1.4 (0.3) |
| PAC Mean Conflict (15mo) | 1.6 (0.7) | 1.6 (0.8) | 1.7 (0.6) |
| PAC-P Mean Conflict (baseline) | 1.4 (0.5) | 1.7 (0.7) | 1.7 (0.6) |
| PAC-P Mean Conflict (6mo) | 1.7 (0.8) | 1.7 (0.8) | 1.4 (0.4) |
| PAC-P Mean Conflict (15mo) | 1.7 (0.8) | 1.6 (0.8) | 1.4 (0.5) |

**Abbreviations**. mg; milligrams; M, mean; SD, standard deviation; CDI, Children's Depression Inventory; BDI, Beck Depression Inventory; QoL, quality of life; NOE, negative outcome expectancy; PT, perceived threat; POE, positive outcome expectancy; PAC, Parent-Adolescent Communication; PAC-P, Parent-Adolescent Communication – Parent.

[a] Tukey post-hoc analyses indicated 6-MP dosage was significantly lower for those in the optimal adherence group compared to those in the moderate adherence group at baseline, 6mo, and 15mo ($p < 0.05$).

[b] Tukey post-hoc analyses also indicated 6-MP dosage was significantly higher for those in the moderate adherence group compared to those in the chronically non-adherent group at baseline ($p < 0.05$).

[c] Tukey post-hoc analyses indicated that youth in the optimal adherence group reported higher positive outcome expectancy than those in the moderate adherence group at baseline ($p = 0.031$).

[d] Tukey post-hoc analyses indicated that youth in the optimal adherence group reported more frequent communication at 15 months than those in the chronically non-adherent group ($p = 0.017$).

Table 6. Correlations Between Dependent Variable (Adherent vs. Non-Adherent Group) and Potential Baseline Covariates

| | Study Group | Age Group | Adolescent Gender | Ethnicity Race | Household Composition | Maternal Education | Household Income | Diagnosis duration |
|---|---|---|---|---|---|---|---|---|
| Age Group | 0.06 | - | | | | | | |
| Adolescent Gender | 0.04 | .17* | - | | | | | |
| Race and Ethnicity | -0.01 | 0.11 | 0.02 | - | | | | |
| Household Composition | -.17* | -0.05 | -0.09 | -.34** | - | | | |
| Maternal Education | -0.001 | -0.04 | 0.03 | -.59** | 0.17 | - | | |
| Household Income | -0.05 | -0.12 | -0.06 | -.59** | .46** | .65** | - | |
| Time since dx | 0.13 | -0.01 | -.38** | 0.10 | -0.05 | -0.14 | -0.02 | - |
| Adherence Group | -0.01 | -.26** | -0.03 | 0.03 | 0.14 | -0.06 | 0.07 | 0.05 |

**Abbreviations.** mg, milligrams; dx, diagnosis; **Notes.** *Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

Table 7. Logistic Regression Models Predicting Adherence Group Membership Outcomes (Aim 2a)

| | Child-Reported Communication Model | | | | Caregiver-Reported Communication Model | | | |
|---|---|---|---|---|---|---|---|---|
| | $\chi^2$ | Odds Ratio | 95% CI | p | $\chi^2$ | Odds Ratio | 95% CI | p |
| Time | **5.08** | **1.00** | **1.0 - 1.0** | **0.02** | 2.31 | 1.00 | 1.0 - 1.0 | 0.13 |
| 6MP Dosage | **5.25** | **1.00** | **1.0 - 1.0** | **0.02** | **4.09** | **1.00** | **1.0 - 1.0** | **0.04** |
| Age Group | **7.41** | **0.25** | **0.09 - 0.68** | **<0.01** | **7.08** | **0.24** | **0.08 - 0.68** | **<0.01** |
| # of Younger Kids in Home | 0.46 | 0.86 | 0.57 - 1.32 | 0.50 | 0.92 | 0.80 | 0.52 - 1.26 | 0.34 |
| NOE | 1.80 | 1.00 | 1.0 - 1.0 | 0.18 | 1.95 | 1.00 | 1.0 - 1.0 | 0.16 |
| POE | 3.08 | 1.00 | 1.0 - 1.0 | 0.08 | **5.16** | **1.00** | **1.0 - 1.0** | **0.02** |
| Intent | 3.40 | 1.00 | 1.0 - 1.0 | 0.07 | 1.70 | 1.00 | 1.0 - 1.0 | 0.19 |
| Communication Frequency | 1.45 | 1.00 | 1.0 - 1.0 | 0.23 | 2.47 | 1.00 | 1.0 - 1.0 | 0.12 |

**Abbreviations**. 6MP, 6-mercaptopurine; #, number; NOE, Negative Outcome Expectancy subscale; POE, Positive Outcome Expectancy. **Notes**. Age group and number of younger kids in home utilized baseline data; time, 6MP dosage, NOE, POE, Intent, Communication Frequency utilized baseline, 6 month, and 15 longitudinal data.

Table 8. Differences in Independent Variables by Age Group

| | Pre-adolescence (7-10 years) | Early-Middle Adolescence (10-15 years) | Middle-Late Adolescence (15-19 years) |
|---|---|---|---|
| Dosage, mg (Baseline) | 71.32 (32.74) | 87.92 (38.91) | **108.54 (46.30)[a]** |
| Dosage, mg (6 mos) | 76.33 (25.83) | 93.42 (42.85) | **121.25 (48.22)[a]** |
| Dosage, mg (15 mos) | **82.07 (30.12)[b]** | 104.86 (48.11) | **136.16 (42.40)[a]** |
| # of Younger Kids in Home (Baseline) | 0.82 (0.90) | 1.04 (0.92) | 0.75 (1.06) |
| NOE (baseline) | 31.41 (13.08) | 29.63 (11.67) | **37.05 (13.59)[c]** |
| NOE (6 mos) | 28.98 (13.93) | 29.85 (12.33) | 33.70 (13.74) |
| NOE (15 mos) | 30.40 (14.42) | 30.40 (14.42) | 30.40 (14.42) |
| POE (baseline) | 118.92 (15.20) | 115.54 (13.01) | 114.56 (14.89) |
| POE (6 mos) | 117.60 (13.32) | 115.00 (20.47) | 116.03 (14.4) |
| POE (15 mos) | 117.02 (15.40) | 117.21 (16.14) | 116.35 (15.67) |
| Intent (baseline) | 43.84 (5.16) | 44.63 (4.04) | 43.76 (6.32) |
| Intent (6 mos) | 44.00 (5.83) | 45.35 (4.25) | 44.80 (5.67) |
| Intent (15 mos) | 43.72 (5.69) | 44.64 (4.79) | 45.26 (5.14) |
| Child Total Communication (baseline) | 15.82 (11.27) | 13.54 (8.93) | 12.93 (10.9) |
| Child Total Communication (6 mos) | 15.81 (11.47) | 11.78 (7.76) | 11.68 (8.94) |
| Child Total Communication (15 mos) | **15.70 (10.88)[d]** | 10.49 (9.43) | 8.82 (8.11) |
| Caregiver Total Communication (baseline) | 16.69 (12.75) | 14.05 (10.98) | 18.40 (13.12) |
| Caregiver Total Communication (6 mos) | 17.95 (14.02) | 13.10 (10.82) | 15.13 (12.69) |
| Caregiver Total Communication (15 mos) | 16.65 (12.21) | 12.67 (12.39) | 13.24 (11.35) |

**Abbreviations**. mg, milligrams; mos, months; #, number; NOE, Negative Outcome Expectancy subscale; POE, Positive Outcome Expectancy.

Table 9. Logistic Regression Models Predicting Adherence Group Membership Outcomes (Aim 3)

| | Total HRQoL Child-Reported Communication Model | | | | Total HRQoL Caregiver-Reported Communication Model | | | |
|---|---|---|---|---|---|---|---|---|
| | $\chi^2$ | Odds Ratio | 95% CI | *p* | $\chi^2$ | Odds Ratio | 95% CI | *p* |
| Time | 3.3 | 1 | 1.0 - 1.0 | 0.07 | **4.22** | **1** | **1.0 - 1.0** | **0.04** |
| 6MP Dosage | **4.4** | **1** | **1.0 - 1.0** | **0.04** | **4.37** | **1** | **1.0 - 1.0** | **0.04** |
| Age Group | **5.25** | **0.28** | **0.09 - 0.83** | **0.02** | **5.25** | **0.28** | **0.09-0.83** | **0.02** |
| # of Younger Kids | 0.64 | 0.84 | 0.55 - 1.29 | 0.42 | 0.64 | 0.84 | 0.55 - 1.29 | 0.42 |
| POE | **4.37** | **1** | **1.0 - 1.0** | **0.04** | **4.71** | **1** | **1.0 - 1.0** | **0.03** |
| Total PedsQL | 0.33 | 1 | 1.0 - 1.0 | 0.57 | 0.29 | 1 | 1.0 - 1.0 | 0.59 |
| | Nausea HRQoL Child-Reported Communication Model | | | | Nausea HRQoL Caregiver-Reported Communication Model | | | |
| | $\chi^2$ | Odds Ratio | 95% CI | *p* | $\chi^2$ | Odds Ratio | 95% CI | *p* |
| Time | 2.44 | 1 | 1.0 - 1.0 | 0.12 | 3.47 | 1 | 1.0 - 1.0 | 0.06 |
| 6MP Dosage | **4.17** | **1** | **1.0 - 1.0** | **0.04** | **4.43** | **1** | **1.0 - 1.0** | **0.04** |
| Age Group | **5.96** | **0.26** | **0.09 - 0.76** | **0.01** | **5.96** | **0.26** | **0.09-0.76** | **0.01** |
| POE | 3.79 | 1 | 1.0 - 1.0 | 0.053 | **4.28** | **1** | **1.0 - 1.0** | **0.04** |
| Nausea PedsQL | 31 | 1 | 1.0 - 1.0 | 0.58 | 1.14 | 1 | 1.0 - 1.0 | 0.29 |

**Abbreviations**. HRQoL, Health-Related Quality of Life; CI, confidence; 6MP, 6-mercaptopurine; #, number; POE, positive outcome expectancy; PedsQL, Pediatric Quality of Life measure. **Notes**. Age group and number of younger kids in home utilized baseline data; time, 6MP dosage, Total PedsQL utilized baseline, 6 month, and 15 longitudinal data.

Table 10. Independent Variable Included in mixed ANOVAs

| | Child Total QoL | Caregiver Total QoL | Child Nausea QoL | Caregiver Nausea QoL |
|---|---|---|---|---|
| Timepoint | x | x | x | x |
| Adherence Group | x | x | x | x |
| Income | x | x | | x |
| Maternal Education | x | x | x | |
| Gender | | x | | x |
| Age Group | | x | | x |
| Ethnicity + Race[a] | x | | | |
| Race | | | x | |
| # of People in Home | x | | | |
| Study Group | | | x | |
| House Composition[b] | | | | x |

**Abbreviations**. QoL, Quality of Life; #, number.

**Notes**. Variables included in each model were significantly correlated ($p < 0.05$) at least at one timepoint (0, 6, 15 months). Baseline demographic data was utilized for income, maternal education, gender, age group, ethnicity + race, race, # of people in the home, study group, and house composition.

[a] Variable capturing both ethnicity and race. Three possible categories: (1) Latinx, (2) non-Latinx racially minoritized, (3) non-Latinx white.

[b] Composition of caregivers (i.e., one or two parent household).

Figure 1. Group-based trajectories for adherence, measured by electronic monitoring, from baseline to 15 months ($N$ = 131).

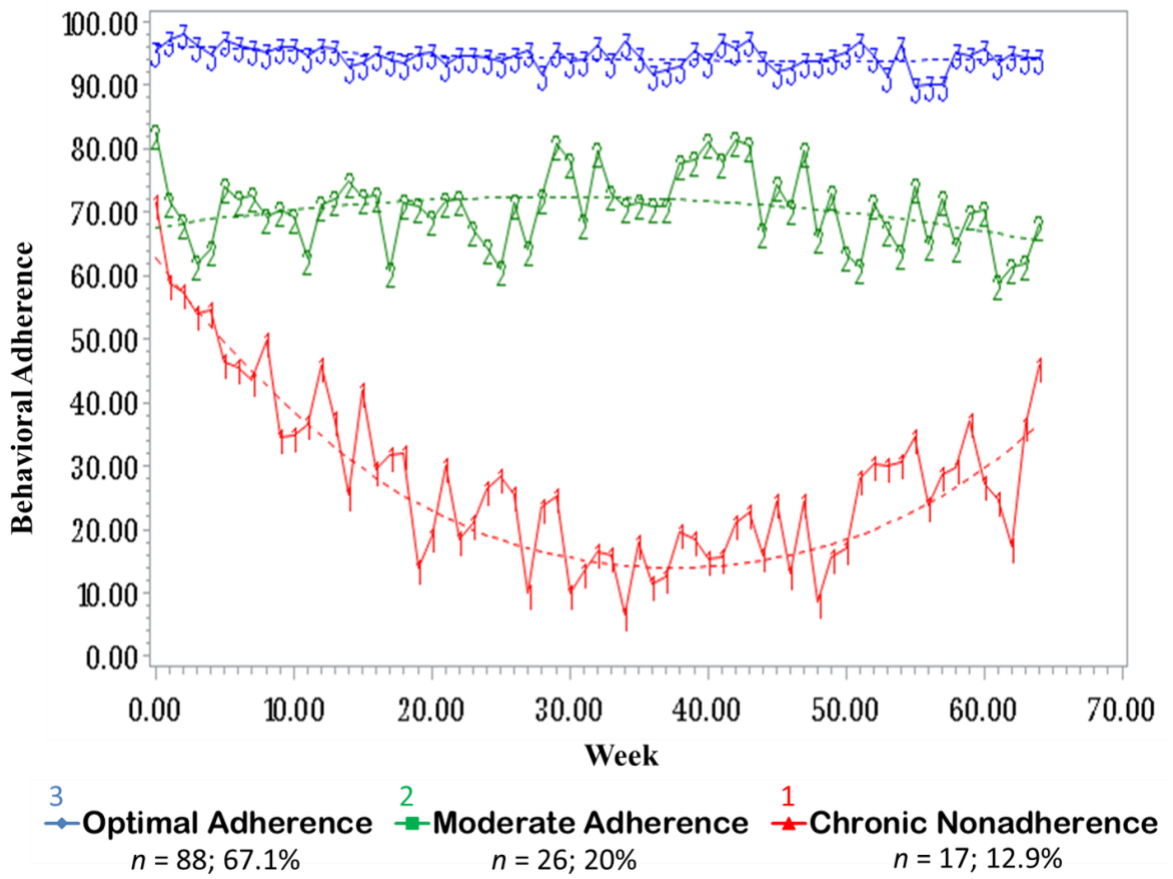


Figure 2. Percentage of Youth in Age Groups (within Adherence Group)

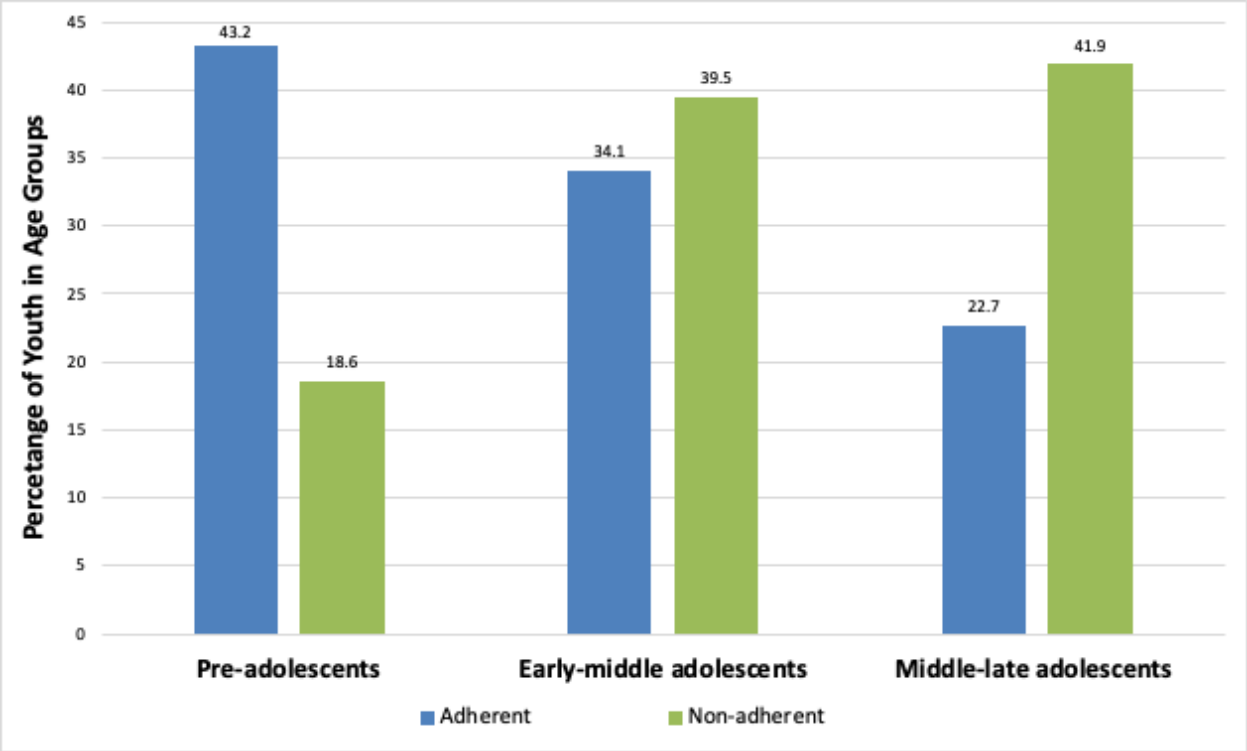



Figure 3. Dosage (mg) Across Adherence Groups

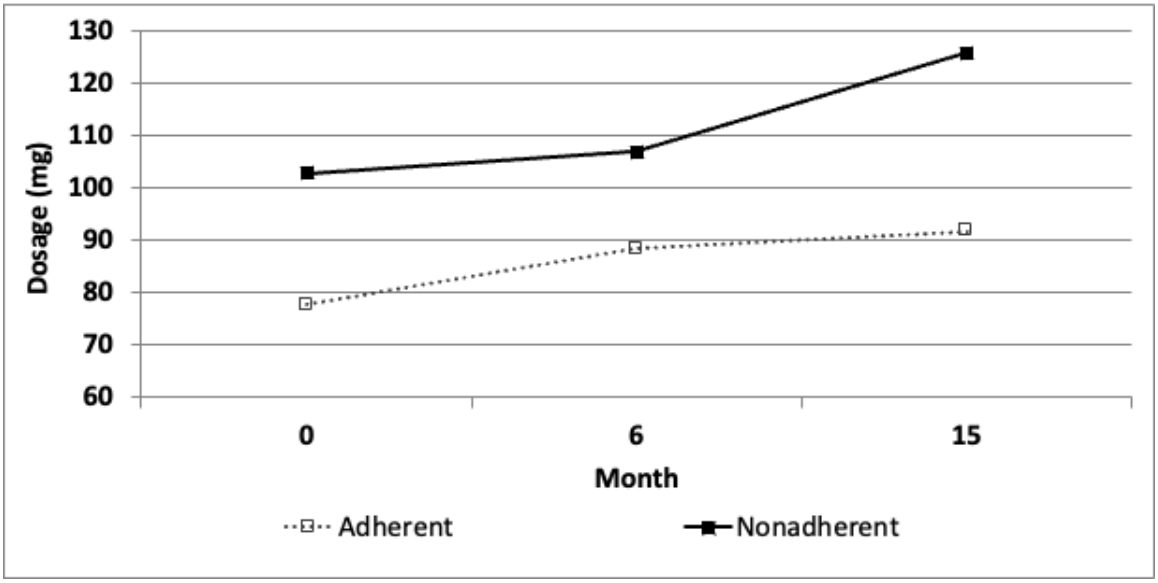


Figure 4. Negative Outcomes Expectancy Across Adherence Groups

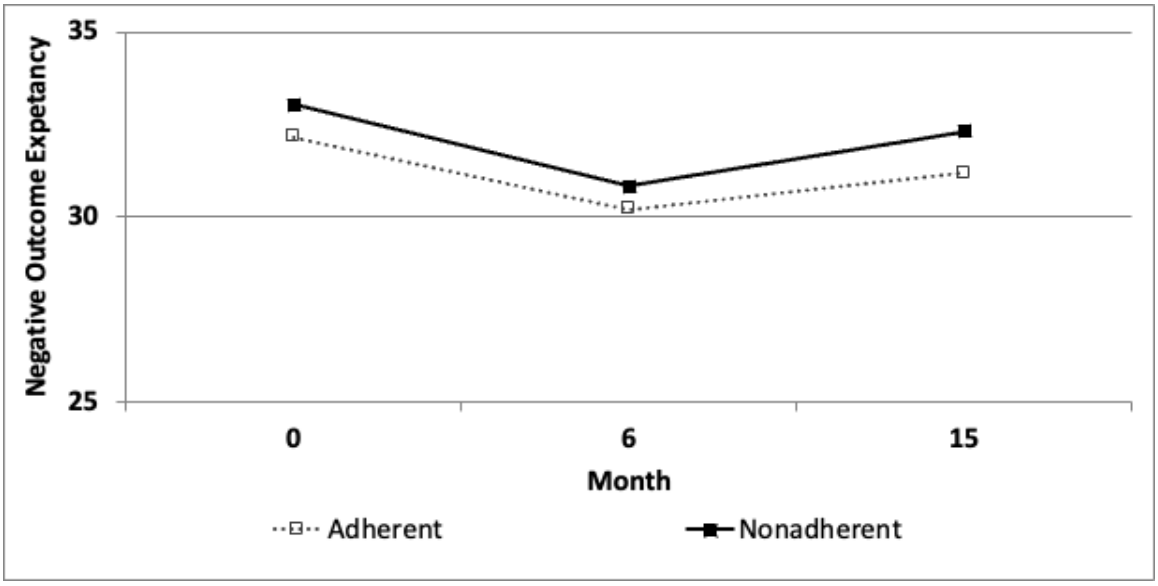



Figure 5. Positive Outcomes Expectancy Across Adherence Groups

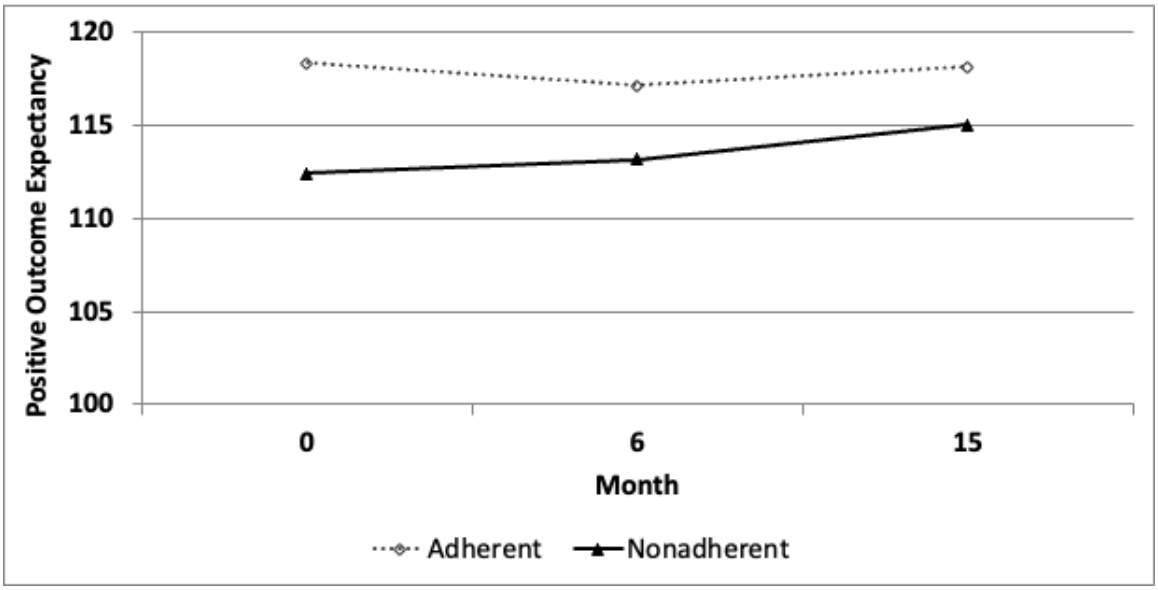


Figure 6. Intent Across Adherence Groups

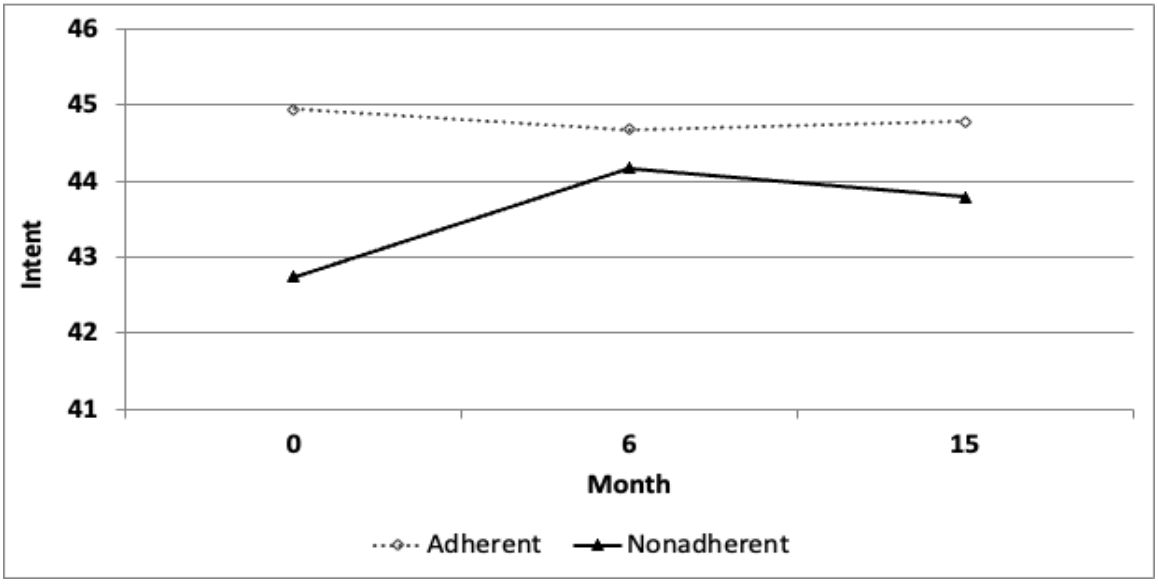



Figure 7. Child-Reported Total Communication Frequency Across Adherence Groups

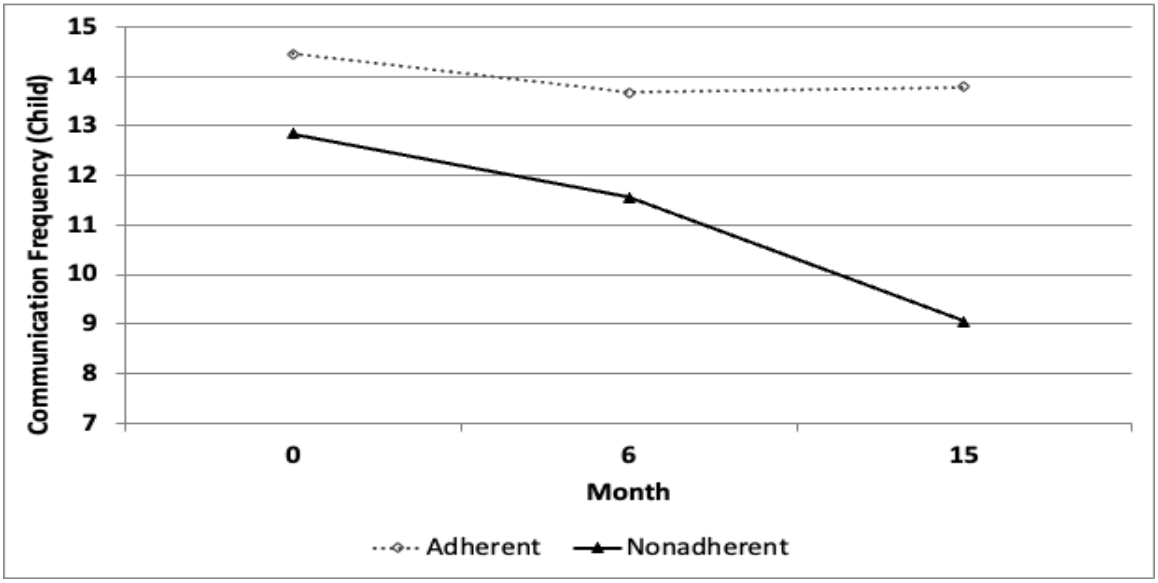


Figure 8. Caregiver-Reported Total Communication Frequency Across Adherence Groups

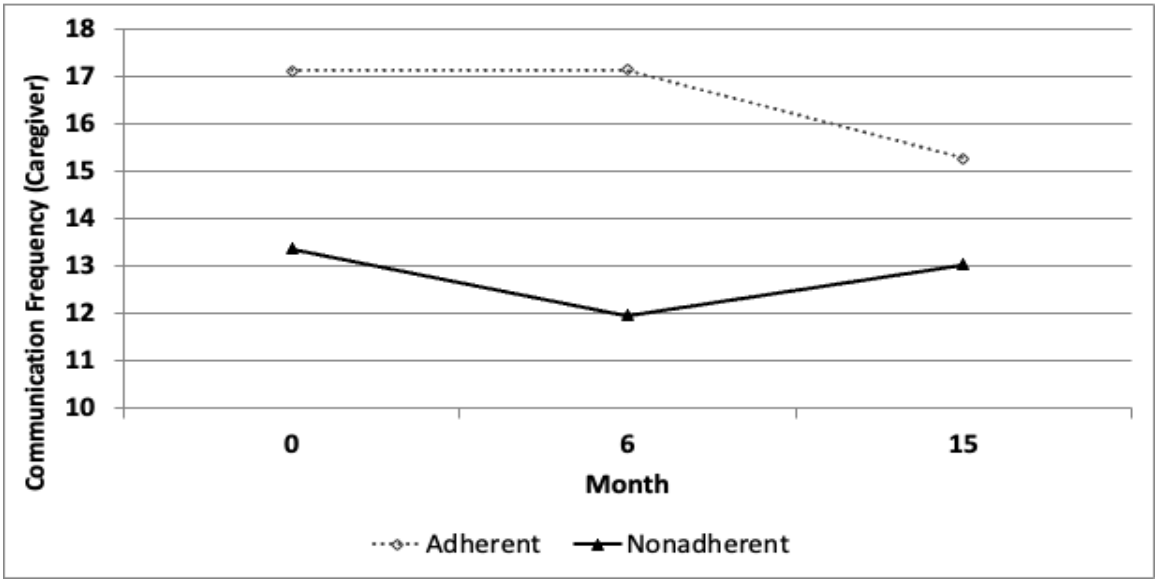



Figure 9. Caregiver-Reported Average Communication Intensity Across Adherence Groups

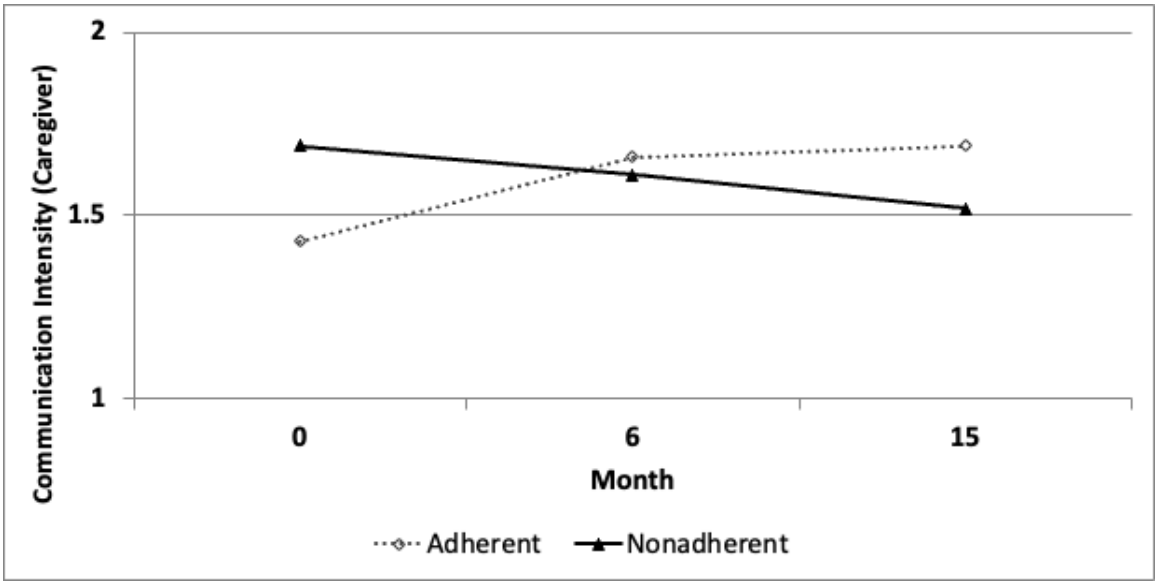


Figure 10. Child-Reported Total HRQoL Across Adherence Groups

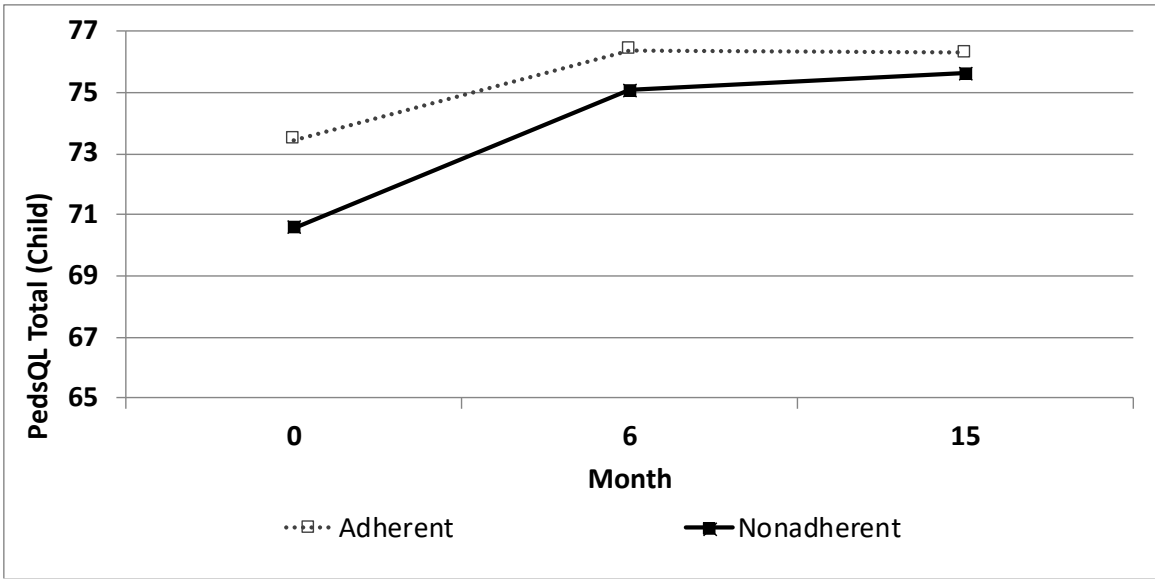



Figure 11. Caregiver-Reported Total HRQoL Across Adherence Groups

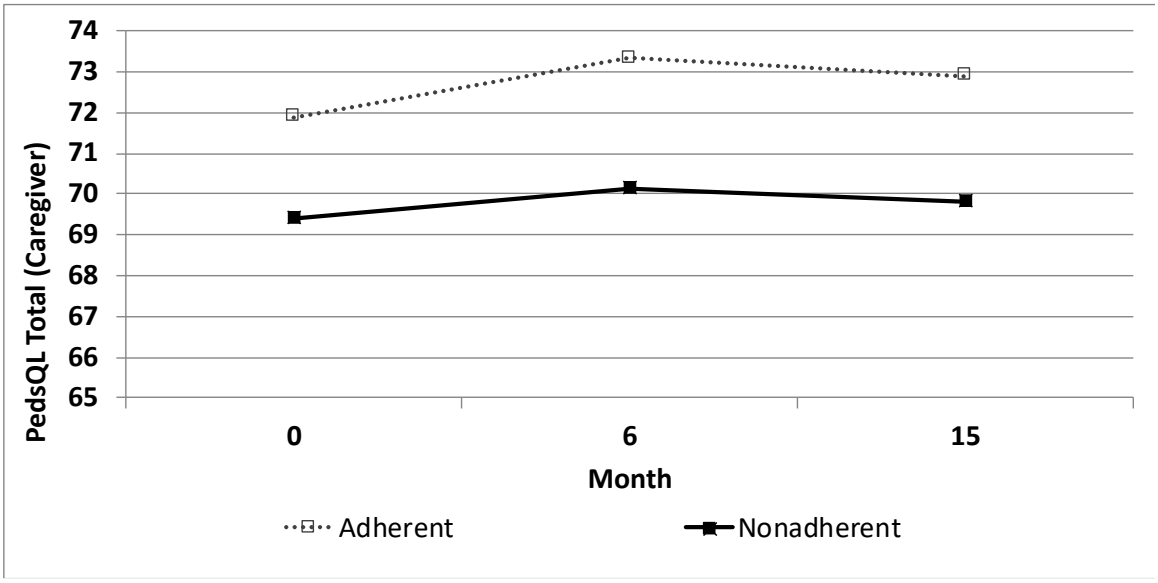


Figure 12. Child-Reported Nausea HRQoL Across Adherence Groups

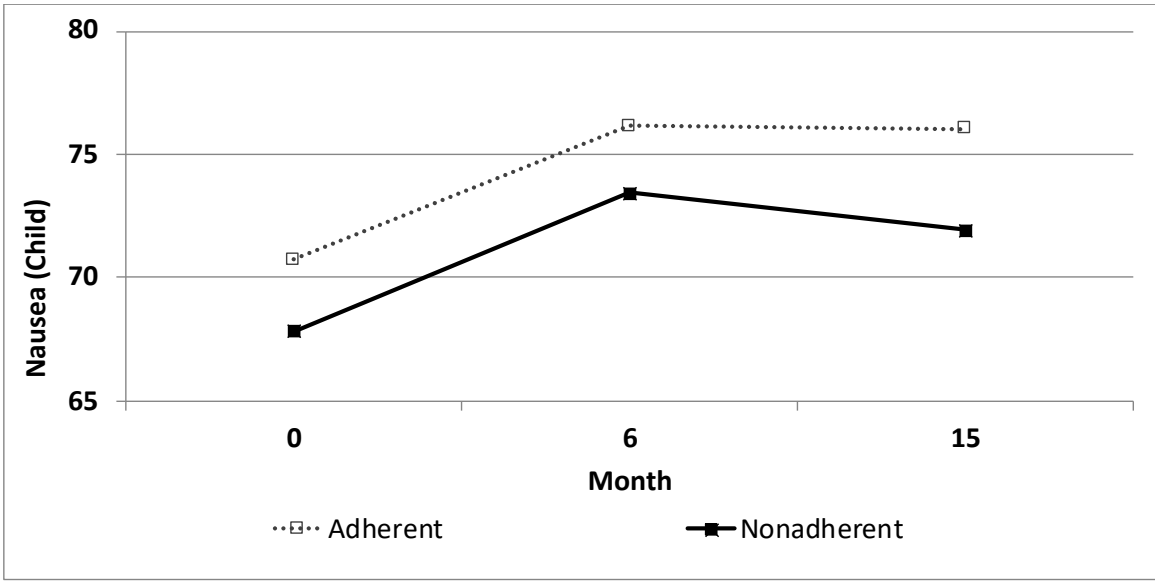
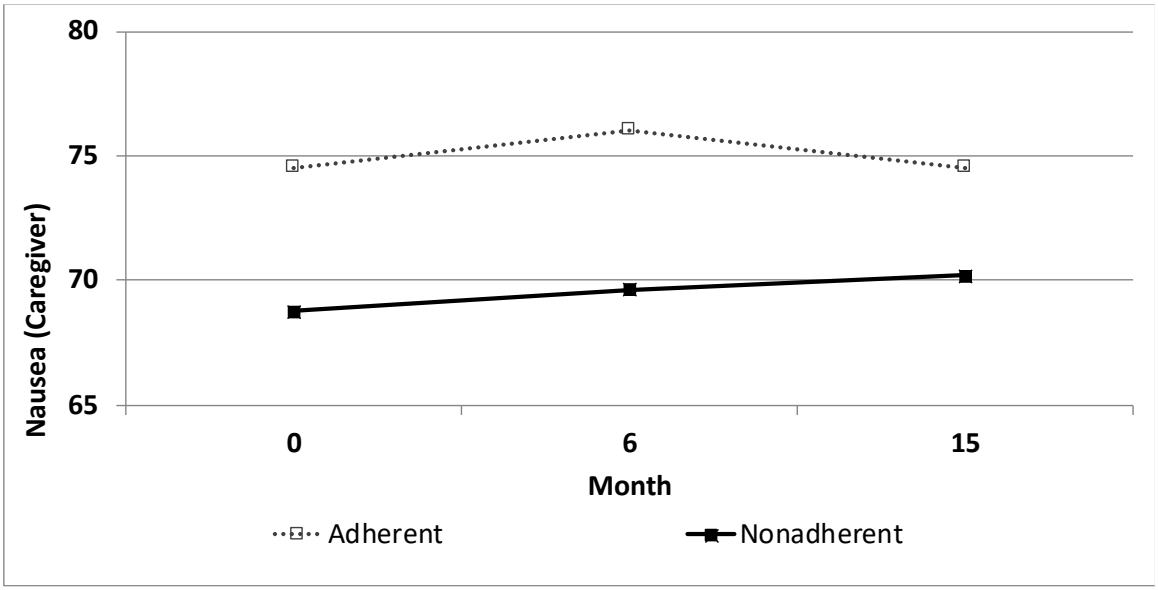



Figure 13. Caregiver-Reported Nausea HRQoL Across Adherence Groups



Appendix A. Interviewer Instructions for PedsQL Young Child (5-7) Report

# PedsQL™

## Cancer Module

Version 3.0

**YOUNG CHILD REPORT** (ages **5-7**)

Instructions for interviewer:

**I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you**.

Show the child the template and point to the responses as you read.

If it is not at all a problem for you, point to the smiling face

**If it is sometimes a problem for you, point to the middle face**

**If it is a problem for you a lot, point to the frowning face**

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

| | Not at all | Sometimes | A lot |
|---|---|---|---|
| Is it hard for you to snap your fingers | ☺ | 😐 | ☹ |

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

Appendix B. Interviewer Instructions for PedsQL Young Child (5-7) Report

Instructions:

Think about how you have been doing for the past one month. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

# How much of a problem is this for you?

Not at all

Sometimes

A lot

Appendix C. Original Study Document Regarding Changes to Beliefs about Medication Measure Administration for Younger Participants (<11years)

**Notes Regarding OPTIMAL Forms for Younger Participants**

We have noticed at our site that our younger study participants are having difficulty both reading and understanding some of the assessments that we administer.

In particular, it seems they struggle more with the SPSI and the BAMS. For this reason, it will be beneficial to administer these questionnaires in an interview format (read questions and write down their responses) for participants under 11 years old.

The language seems to be advanced for our younger participants, so it is also a good idea to paraphrase some of the more complex questions.

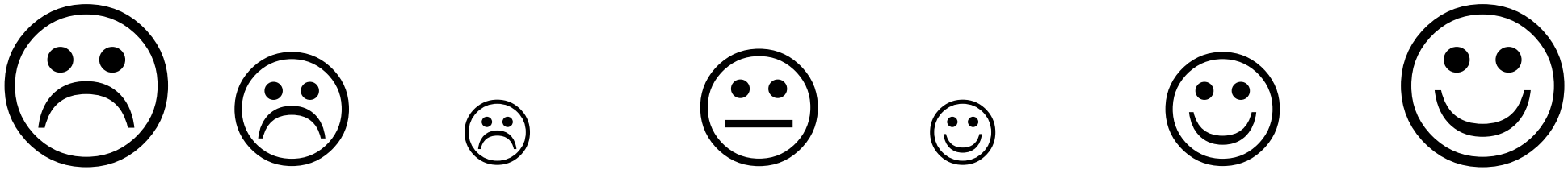
The following are some specific questions and examples of how to paraphrase them from the BAMS:

- Q. 29 “Other people with my illness get very sick even if they take their medicine the way the doctor says they should.” Paraphrase, “Other kids with cancer get very sick even when they take their medicine the right way.”
- Q. 30 “I have a lot to gain from taking my medicine the way the doctor says I should.” Paraphrase: “It will be good for me to take my medicine like the doctor says I should.”
- Q. 35 “If I take my medicine the way the doctor says I should, it will keep me from getting sicker.” Paraphrase: “I won’t get sicker if I take my medicine like the doctor says.”

Appendix D. Visual Diagram Used with Younger Participants (<11years) for Beliefs about Medicine Scale (BAMS) – Child Version

## Visual Diagram to be used during Interview Administration

PLEASE RATE HOW MUCH **YOU** AGREE ☺ OR DISAGREE ☹ WITH EACH STATEMENT USING THE FOLLOWING RATING SCALE:



| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **Disagree a Lot** | **Disagree Mostly** | **Disagree a Little** | **Don't Agree nor Disagree** | **Agree a Little** | **Agree Mostly** | **Agree a Lot** |

# Vita

Stephanie Romo was born on August 16, 1992, in Hialeah, Florida. She graduated from Miami Springs Senior High School, Miami Springs, Florida in 2010. She received her Bachelor of Arts in Psychology from New York University, New York, New York in 2014 and subsequently worked for Shriners Hospitals for Children—Boston and Massachusetts General Hospital for three years before starting her graduate studies in the Clinical Psychology Doctoral Program at Virginia Commonwealth University in August of 2017. She earned her Master of Science in Psychology from Virginia Commonwealth University in May of 2020.