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Samantha Gagnon Date

**Health-related quality of life among multiple myeloma patients treated with CAR-T therapy**

By

Samantha Gagnon

Master of Public Health

Applied Epidemiology

Executive Master of Public Health

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Jeffrey Switchenko, PhD
Committee Chair

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Ajay Nooka, MD, MPH
Committee Member

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By

Samantha Gagnon

B.S., University of South Florida, 2012

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Thesis Committee Chair: Jeffrey Switchenko, PhD

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Master of Public Health in Applied Epidemiology

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**Abstract**

**Health-related quality of life among multiple myeloma patients treated with CAR-T therapy**

By Samantha Gagnon

**Background:** Multiple myeloma (MM) is the second most common hematologic malignancy, with 34,000 new cases diagnosed in the United States annually. There is currently no cure for MM, though treatment options have expanded exponentially in the last few decades, and significantly improved overall survival, with a 5-year relative survival rate of 57.9%. In this context, adoptive cellular therapies have shown to be a feasible and effective treatment option for patients who are refractory to the commonly used antimyeloma agents. Recently, chimeric antigen receptor T-cell (CAR-T) therapy targeting the B-cell maturation antigen (BCMA) has seen improved clinical outcomes (PFS and OS) in treating relapsed/refractory multiple myeloma (RRMM). Positive outcomes and recent Food and Drug Administration (FDA) approval has seen a need for more data on CAR-T effects on health-related quality of life (HRQL).

**Objective:** The primary purpose of this pilot study is to investigate predictors of HRQOL measurements among MM patients, without disease progression, who have been treated with CAR-T therapy. Patients and clinicians may utilize the results of this study to make informed treatment decisions and to identify supportive intervention needs for HRQOL improvement in the study population.

**Methods:** HRQOL measurements were obtained by study personal using validated tool, self-administered FACT-MM questionnaire post-CAR-T infusion between December 14, 2021, and July 25, 2022. Subjects included in analysis had received CAR-T for treatment of MM a minimum of 56 days prior to survey date and had not yet experienced progression of disease as defined by the International Myeloma Working Group (IMWG) criteria. The primary endpoint measurement was the FACT-MM composite score. Associations between FACT-MM scores and predictors which included demographics, disease and treatment history, and comorbidities were analyzed using nonparametric tests due to left-skewed distribution. FACT-MM and subscores were analyzed as continuous and dichotomous outcomes.

**Results:** The study population included twenty-two patients, with a median FACT-MM score of 137.5 (range: 88-156) out of maximum possible 164 points. There was no significant difference in HRQOL measurements between sex, age groups, years since diagnosis, ISS staging, CCI score, or time since infusion. Statistically significant differences in HRQOL measurements including overall FACT-MM, and subscores including myeloma specific, physical well-being and pain side effects were observed between races, certain comorbidities, different therapy class exposures and number of lines of prior therapy.

**Conclusion:** Patients treated with CAR-T have relatively high levels of HRQOL at least 2 months out from infusion. Significant findings were limited, though due to the extremely small sample size of this pilot study, the results obtained warranted an expansion of the pilot and further study.

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**Table of Contents**

## Chapter 1: Background and literature review

Multiple myeloma (MM or myeloma) is a hematologic malignancy of clonal plasma cells, originating from the post-germinal lymphoid B-cell lineage, proliferating in the bone marrow (Palumbo & Anderson, 2011). Myeloma is associated with a heavy physical symptom burden, stemming from end-organ damage and cumulative toxicities from treatments. Newly diagnosed patients may present with fractures, chronic musculoskeletal pain, renal insufficiency, anemia, or hypercalcemia (Rajkumar, 2020). Inherently, the burden associated with the disease related symptoms lends itself to potentially lower self-reported health-related quality of life (HRQOL). Higher symptom burden has been associated with lower HRQOL (Rajkumar, 2020). In addition to the physical manifestations noted above, newly diagnosed patients may experience psychosocial distress related to the disruption of their everyday life. There is currently no curative treatment for myeloma, thus the majority of individuals experience refractory response to either frontline or salvage therapy or relapsed disease following a positive disease response. This condition is referred to as relapsed/refractory multiple myeloma (RRMM).

Despite the lack of curative options for multiple myeloma, treatment options have expanded exponentially in the last few decades, leading to major improvements in progression free (PFS) and overall survival (OS) rates. According to the National Cancer Institute (NCI) (2022), the current 5 year survival rate in the United States (U.S.) for MM is approximately 57.9%, more than doubling from just 28% in 1975 (Hemminki et al., 2021). Current drug regimens that led to such drastic improvements include immunomodulators (IMiDs), proteasome inhibitors (PIs), anti-CD38 monoclonal antibodies (mabs), and autologous stem cell transplants (Martino et al., 2021). With relapses or refractory responses common in myeloma, patients may exhaust standard of care treatment options. In this context, adoptive cellular therapies have

shown to be a feasible and effective treatment option for patients who are refractory to the commonly used antimyeloma agents.

Though objective endpoints such as PFS and OS have seen improvement with the treatment advances, ongoing side-effects of the disease, treatment toxicities, and socioeconomic burdens continue to result in lower patient-reported health-related quality of life for MM patients, when compared to other hematologic malignancies (Zaleta et al., 2020). This review will address the epidemiology of multiple myeloma, benefits of cellular therapies in the multiple myeloma population, and the role of health-related quality of life data in clinical decision making.

*Epidemiology of multiple myeloma*

Multiple myeloma is rare, with only a 0.8% lifetime risk according to the NCI (2022), but it is the second most common hematologic malignancy in high-income countries (Huang et al., 2022). The incidence is greater than 34,000 diagnoses annually in the United States, accounting for approximately 13% of all hematologic malignancies (Cowan et al., 2022; Palumbo & Anderson, 2011). Multiple myeloma is part of a family of plasma dyscrasia disorders, arising from monoclonal gammopathy of unknown significance (MGUS). The disease may lay dormant and unnoticed for years as MGUS or smoldering multiple myeloma (SMM) (Atkin et al., 2018). With MGUS and SMM, there is approximately 1% and 1-10% annual risk of progression to symptomatic myeloma respectively (Mann et al., 2022; Rajkumar, 2015). Due to the asymptomatic nature of MGUS and SMM, myeloma is often not diagnosed until it is symptomatic.

The NCI age-adjusted MM mortality rate for the U.S. is 3.2 per 100,000 which is 12,640 myeloma-related deaths in 2022. In line with the global trend of a rapidly aging population, the global incidence of myeloma increased by 126% and mortality increased by 94% between 1990 and 2016 according to the Global Burden of Disease Study (Cowan et al., 2018).

The global incidence of myeloma is approximately 176,000 and approximately 113,000 deaths annually, but these rates vary widely across geographic areas (Palumbo & Anderson, 2011; Zhou et al., 2021). Higher gross domestic product (GDP) per capita has been associated with increased incidence in both men and women, with the highest incidences of MM identified in Australia, North America, and Western Europe respectively (Huang et al., 2022). Socio-demographic index (SDI) has also been associated with differences in incidence and mortality. Mortality rates have trended downwards globally in the past 2 decades, but areas with higher SDI have seen larger decreases, which is likely due to greater advances in medical technology and wide availability of supportive care and antimyeloma treatment options in those areas compared to areas with lower SDI (Zhou et al., 2021).

In addition to incidence and mortality rates, researchers may use disability-adjusted life years (DALYs) to fully explain the burden of multiple myeloma. The World Health Organization defines DALYs as "a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability." Globally, DALY burden is varying, according to the Institute of Health Metrics and Evaluation (IHME) (2022). The global DALYs rate for multiple myeloma in 2019 was 2.32 per 100,000, while the U.S. rate was significantly higher, at 11.33 per 100,000, per the IHME's Global Burden of Disease data (2022).

Incidence rates also vary by age, sex, and racial groups. Multiple myeloma is more often diagnosed in older individuals, with an average age at diagnosis of 69 years old and only 13.2% of diagnoses occurring under the age of 55 (National Cancer Institute, 2022). Men are more likely to be diagnosed with MM, with an incidence rate of 8.8 per 100,000 compared to 5.9 per 100,000 in women (NCI, 2022). The global incidence rate has remained steady among According to NCI SEER data (2019), the highest age-adjusted incidence is in non-Hispanic Black individuals, at 16.1 per 100,000. Hispanics have only slightly higher incidence than non-Hispanic white Americans, with 7.1 per 100,000, while the lowest incidence rates are found in American Indians/Alaskan Natives (6.6 per 100,000) and Asians (4.7 per 100,000).

*Chimeric Antigen Receptor T Cell therapy for relapsed/refractory multiple myeloma*

Chimeric antigen receptor T-cell (CAR-T) therapy is an adoptive cellular treatment modality in which genetically engineered chimeric antigen receptor proteins are transduced into autologous T-cells, meant to target disease-specific tumor markers (Haslauer et al., 2021; Sermer & Brentjens, 2019). The first FDA approved CAR-T product, tisagenlecleucel-T, was approved in 2017 for relapsed/refractory acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) (Haslauer et al., 2021). In 2013, researchers first evaluated the efficacy of CAR-T therapy targeting the B-cell maturation antigen (BCMA) for treating relapsed/refractory multiple myeloma (Carpenter et al., 2013). Since that time, multiple clinical trials evaluated BCMA targeting CAR-T product manufactured from autologous T-cells on diverse myeloma populations in the United States and Europe. Clinical trials have focused on the RRMM population, with limited research in the frontline setting. In 2021, the Food and Drug Administration (FDA) approved the first of these products, idecabtagene vicleucel (ide-cel), for

use in RRMM that previously received at least 4 lines of therapy, which must include triple-class exposure to IMiDs, PIs, and anti-CD38 mabs (Jagannath et al., 2021). Ciltacabtagene autoleucel (cilta-cel) approval followed in early 2022, with the same set of prior therapy requirements (Martin et al., 2022).

In ide-cel clinical trials, 73% of patients achieved at least a partial response by IMWG criteria, with 33% achieving a complete response or stringent complete response (Munshi et al., 2021). The patients in the ide-cel clinical trial also achieved a median progression-free survival of 8.8 months. With a median time of 6 years since diagnosis in the trial population, this is a significant duration of response (Munshi et al., 2021). In addition to the potential for treatment free intervals, data from the KarMMa-1 (ide-cel) trial showed a sustained improvement of HRQOL indices including fatigue, pain, and physical functioning through up to 18 months post-infusion (Delforge, et al., 2022).

According to Martin et al. (2022), in cilta-cel trials, 97.9% of patients achieved at least a partial response and 82.5% of patients achieved a stringent complete response. Even with robust overall response rate (ORR) and PFS times, there were variations among the patient populations. In the CARTITUDE-1 (cilta-cel) trial, researchers found high ORR in all patient subgroups, "including those with plasmacytomas, high-risk cytogenetics, and ISS stage III" (Martin et al., 2022). However, Martin et al. (2022) also found that the same patient subgroups with aforementioned high-risk disease characteristics had shorted duration of response, PFS, and OS.

These positive advances in improved clinical outcomes (PFS and OS) from clinical trials have increased the interest in and desirability of treatment with CAR-T therapy. An additional attractive advantage is the perception of CAR-T as a one-time treatment modality allowing for the

majority of patients who achieve a deep response to forego maintenance treatment while in remission.

*Health-related quality of life*

Health-related quality of life has more than one commonly used definition. The International Society for Quality of Life Research (2015) defines HRQOL as, "A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, more specifically HRQOL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions, and opportunities, as influenced by disease, injury, treatment, and policy." Though there are multiple models defining the concept, the term often refers to the patient or observer reported, subjective multi-domain assessment of the impact of a disease and corresponding treatment (Karimi & Brazier, 2016). HRQOL measurements may evaluate physical, psychosocial, spiritual, and functional factors (Bakas, et al., 2012).

As HRQOL is a subjective construct with several accepted models, there is no singular referent tool. Several validated tools have been used to measure HRQOL in oncologic settings, both in clinical trial and standard of care settings. HRQOL tools that have been validated for use with multiple myeloma patients include Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy (FACT-MM) (Wagner, et al., 2012), as well as The European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (EORTC QLQ-C30) and myeloma-specific questionnaire (QLQ-MY20) (Aaronson, et al., 1993; Cock, et al., 2007). Currently, in the myeloma, and more

specifically cellular adoptive therapy space, there is still a deficit in evidence of the impact of treatment on HRQOL, and how the HRQOL changes may affect treatment outcomes.

Myeloma treatment outcomes are commonly measured by clinical evidence of disease improvement, but HRQOL surveys allow for assessment of the unseen factors that are also integral to patient success. The subjective aspect of HRQOL reflects the heterogenous makeup of the multiple myeloma patient population. There has been more research done regarding HRQOL and patient outcomes in the newly diagnosed population versus the relapsed refractory multiple myeloma (RRMM) patient population (Niclsen, et al., 2017) As there is still no curative treatment in the myeloma population, most patients will eventually fall into the RRMM category, indicating a need for more focus on HRQOL in the group.

In oncology, treatments and outcomes are constantly evolving based on both therapeutic and non-therapeutic research. Despite the ability to tell clinicians much about non-clinical outcomes, HRQOL is not routinely studied in trials. According to Mohyuddin et al., (2021) HRQOL was a secondary or exploratory endpoint in only 19.9% of randomized clinical trials for myeloma published between 2005 and 2019, and a primary endpoint in only three (2%) of the 151 trials analyzed. HRQOL differences among oncology patients have been correlated with the duration of the disease (Stickel & Goerling, 2018). There is little evidence of HRQOL improvements as disease duration and treatment lines increase, as some side effects from antimyeloma drugs are irreversible and cumulative. Time between relapses typically shortens on each subsequent relapse. This is an important statistic in the CAR-T population, as the median lines of prior therapy was 6 in both ide-cel and cilta-cel clinical trials, and FDA approval is for patients who have been treated with 4 lines or more (Berdeja et al., 2021; Munshi et al., 2021)

With only 36% of patients diagnosed under the age of 65, the majority of patients are elderly, may not be suitable for clinical trials, and may have significant associated comorbidities (National Cancer Institute, 2022). Elderly individuals with myeloma are at risk of being both under and over-treated, leading to concerns about frailty and quality of life (Antoine-Pepeljugoski & Braunstein, 2019). Older adult myeloma patients have been found to have the lowest HQROL outcomes among survivors of all cancer sites (Kent et al., 2015). As treatments continue to become more individualized, HRQOL data can bridge the knowledge gap outside of clinical data, allowing for clinicians to treat the patient's psychosocial and functional needs, regardless of their age. Approximately 40% of MM patients do not criteria for phase-3 clinical trials, which leads to lack of data, both clinical and HRQOL, and underlines the importance of observational HRQOL research in real-world patient populations. (Terpos, et al., 2021)

*Problem Statement*

There is a dearth of information regarding the effects of the novel treatment approach, CAR-T therapy, on health-related quality of life among patients with multiple myeloma. Understanding the late effects of CAR-T on HRQOL of myeloma patients will allow not only for devising supportive interventions to improve HRQOL but also aid with clinical and personal decision-making for proceeding with CAR-T in the first place.

*Purpose*

This cross-sectional, pilot observational study aimed to investigate the late effects of CAR-T therapy on health-related quality of life in multiple myeloma patients over the age of 18 who were treated at Emory University Hospital and remained free of disease progression beyond 2 months (56 days) post-treatment. HRQOL was assessed with a validated tool, the Functional Assessment of Cancer Therapy – Multiple myeloma (FACT-MM) scale. FACT-MM is a disease-

specific patient-reported outcome which assesses a subject's physical, social, emotional, and functional well-being, as well as pain and myeloma specific symptoms over the past 7 days (Wagner, et al., 2012). Patients and clinicians may utilize results of this study to determine factors that affect HRQOL in this patient population, identify associations that require further research, and devise interventions and protocols to enhance long-term HRQOL for myeloma CAR-T recipients.

*Significance*

Prior to this study, there is a notable lack of HRQOL data for myeloma CAR-T patients, with published data being correlated specifically to respective clinical trials. Further, as previously noted, there is a dearth of information regarding the lasting effects of CAR-T on real-world patient-reported HRQOL. CAR-T therapy remains a relatively novel approach, with BCMA-targeted products first trialed in 2013, and first F.D.A. approval in 2021. Clinical data has shown promise with increases in both progression free survival and overall survival; however, some patients may prioritize robust HRQOL over longevity of response when weighing out treatment options. This study will assist clinicians in making treatment decisions and educating patients on potential HRQOL changes. With no curative options currently available for myeloma, the pressure is on for clinicians to weigh out all of the innovative new options available to find the most effective route while still preserving quality of life for patients, who have goals to live life with as little disruption to their normal routine as possible. While CAR-T is an appealing approach in this space, the lack of data related to potential long-term impacts on patient-reported HRQOL outcomes creates a challenge for key stakeholders including practitioners and patients alike.

As this research was undertaken as a pilot study, a primary benefit for stakeholders is that the results obtained will assist in hypothesis generation for future studies on a larger scale. Associations identified in the primary analysis will allow future researchers to identify variables of interest for their own analyses, with potential for longitudinal or multi-site studies. Building off of the results gained from this research, additional longitudinal observational studies may improve validity and clinical usefulness of HRQOL surveys. With limited studies using HRQOL outcomes as endpoints in myeloma clinical trials, the research has potential to discover previously unknown associations, as well as to generate hypotheses that include comparisons of HRQOL effects amongst different treatment options.

## Chapter 2: Manuscript


### Abstract

**Health-related quality of life among multiple myeloma patients treated with CAR-T therapy**

By Samantha Gagnon

**Background:** Multiple myeloma (MM) is the second most common hematologic malignancy, with 34,000 new cases diagnosed in the United States annually. There is currently no cure for MM, though treatment options have expanded exponentially in the last few decades, and significantly improved overall survival, with a 5-year relative survival rate of 55.6%. In this context, adoptive cellular therapies have shown to be a feasible and effective treatment option for patients who are refractory to the commonly used antimyeloma agents. Recently, chimeric antigen receptor T-cell (CAR-T) therapy targeting the B-cell maturation antigen (BCMA) has seen improved clinical outcomes (PFS and OS) in treating relapsed/refractory multiple myeloma (RRMM). Positive outcomes and recent FDA approval has seen a need for more data on CAR-T effects on health-related quality of life (HRQOL).

**Objective:** The primary purpose of this pilot study is to investigate predictors of HRQOL measurements among MM patients, without disease progression, who have been treated with CAR-T therapy. Patients and clinicians may utilize the results of this study to make informed treatment decisions and to identify supportive intervention needs for HRQOL improvement in the study population.

**Methods:** HRQOL measurements were obtained by study personal using validated tool, self-administered FACT-MM questionnaire post-CAR-T infusion between December 14, 2021, and July 25, 2022. Subjects included in analysis had received CAR-T for treatment of MM a minimum of 56 days prior to survey date and had not yet experienced progression of disease as defined by the International Myeloma Working Group (IMWG) criteria. The primary endpoint measurement was the FACT-MM composite score. Associations between FACT-MM scores and predictors which included demographics, disease and treatment history, and comorbidities were analyzed using nonparametric tests due to left-skewed distribution. FACT-MM and subscores were analyzed as continuous and dichotomous outcomes.

**Results:** The study population included twenty-two patients, with a median FACT-MM score of 137.5 (range: 88-156) out of maximum possible 164 points. There was no significant difference in HRQOL measurements between sex, age groups, years since diagnosis, ISS staging, CCI score, or time since infusion. Statistically significant differences in HRQOL measurements including overall FACT-MM, and subscores including myeloma specific, physical well-being and pain side effects were observed between races, certain comorbidities, different therapy class exposures and number of lines of prior therapy.

**Conclusion:** Patients treated with CAR-T have relatively high levels of HRQOL at least 2 months out from infusion. Significant findings were limited, though due to the extremely small sample size of this pilot study, the results obtained warrant an expansion of the pilot and further study.

## Introduction

Multiple myeloma (MM or myeloma) is a hematologic malignancy of clonal plasma cells, originating from the post-germinal lymphoid B-cell lineage, proliferating in the bone marrow (Palumbo & Anderson, 2011). Myeloma is associated with a heavy physical symptom burden, stemming from end-organ damage and cumulative toxicities from treatments. Newly diagnosed patients may present with fractures, chronic musculoskeletal pain, renal insufficiency, anemia, or hypercalcemia (Rajkumar, 2020). Inherently, the burden associated with the disease related symptoms lends itself to potentially lower self-reported health-related quality of life (HRQOL). Higher symptom burden has been associated with lower HRQOL (Rajkumar, 2020). In addition to the physical manifestations noted above, newly diagnosed patients may experience psychosocial distress related to the disruption of their everyday life. There is currently no curative treatment for myeloma, thus the majority of individuals experience refractory response to either frontline or salvage therapy or relapsed disease following a positive disease response. This condition is referred to as relapsed/refractory multiple myeloma (RRMM).

Despite the lack of curative options for multiple myeloma, treatment options have expanded exponentially in the last few decades, leading to major improvements in progression free (PFS) and overall survival (OS) rates. According to the National Cancer Institute (NCI) (2022), the current 5 year survival rate in the United States (U.S.) for MM is approximately 57.9%, more than doubling from just 28% in 1975 (Hemminki et al., 2021). Current drug regimens that led to such drastic improvements include immunomodulators (IMiDs), proteasome inhibitors (PIs), anti-CD38 monoclonal antibodies (mabs), and autologous stem cell transplants (Martino et al., 2021). With relapses or refractory responses common in myeloma, patients may exhaust standard of care treatment options. In this context, adoptive cellular therapies have

shown to be a feasible and effective treatment option for patients who are refractory to the commonly used antimyeloma agents.

Though objective endpoints such as PFS and OS have seen improvement with the treatment advances, ongoing side-effects of the disease, treatment toxicities, and socioeconomic burdens continue to result in lower patient-reported health-related quality of life for MM patients, when compared to other hematologic malignancies (Zaleta et al., 2020). This review will address the epidemiology of multiple myeloma, background, and benefits of cellular therapies in the multiple myeloma population, and the role of health-related quality of life data in clinical decision making.

## Methods

*Data Source*

For this cross-sectional observational study, myeloma patients who had undergone autologous CAR-T therapy at Winship Cancer Institute of Emory, were identified by Emory clinicians, specifically physicians and advanced practice providers. Once identified, the study team screened patients for eligibility and inclusion in the study using electronic medical record (EMR) review. Patients were considered eligible if they were 18 years or older, had a diagnosis of MM, able to read and write English, had been treated for MM with CAR-T at least 2 months (56 days) prior to study enrollment, and had not experienced progression of disease since CAR-T infusion. The study was approved by the Emory University IRB board on December 6, 2021.

Enrolled patients completed the Functional Assessment of Cancer Therapy – Multiple Myeloma (FACT-MM) questionnaire on day of enrollment. Patient demographics, disease characteristics, medical and treatment history, were abstracted by EMR. All surveys were collected using paper copies of FACT-MM as required by FACIT licensure. Deidentified survey

responses, demographic, and clinical data were transferred to secure REDCap database for management.

*HRQOL Measurements*

FACT-MM is a validated survey tool measuring patient-reported outcomes (PRO) of HRQOL, specifically for use in MM patients. FACT-MM is comprised of 41 items which measure physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB), as well as pain and myeloma specific symptoms, as reported by the patient over the past 7 days. Items are grouped by the category under which they apply among the aforementioned types. FACT-MM total score is calculated by the sum of all 41 items. FACT-G is the sum of the items that measure PWB, SWB, EWB, and FWB. Trial Outcome Index (TOI), which is the sum of the PWB and FWB, is commonly used in clinical trials to summarize the physical and functional outcomes from the treatment (FACIT). Multiple myeloma specific (MMS) and pain subscales are composites of items related to the respective categories, as determined by FACIT, and there is some overlap between the items. Lastly, well-being scores (PWB, SWB, EWB, and FWB) are the composites of items in their respective categories. Higher total FACT-MM or sub scores indicate higher health-related quality of life (FACIT). Cut points for FACT-MM and all subscores were determined using the medians of the sample.

*Statistical Methods*

As this was an exploratory, hypothesis-generating pilot study, sample size was determined based on feasibility of collecting an attainable sample size within a fixed period. Outcomes were defined as the HRQOL measurements based off FACT-MM and subscores (FACT-General, Trial Outcome Index, physical well-being, social/family well-being, emotional

well-being, function well-being, pain, and myeloma-specific). Outcomes were analyzed as both continuous and dichotomous, with sample medians defining cut points. Covariates were divided into 4 categories; demographics (sex, race, ethnicity, and age at enrollment), baseline disease characteristics (R-ISS stage, risk stratification, years since MM diagnosis, days since CAR-T infusion, number of prior lines of therapy, prior treatment class exposures, history of bone lesions, and history of extramedullary disease), medical history (hypertension, renal disease, diabetes mellitus type 2, hepatic impairment, cardiac impairment, and Charlson Comorbidity Index (CCI) score), and post-CAR-T characteristics (cytokine release syndrome (CRS) diagnosis, neurotoxicity diagnosis, best disease response, and maintenance therapy).

Descriptive statistics were used to analyze demographics and clinical characteristics and are summarized in Table 1. Frequencies and percentages were calculated for categorical variables, while mean, median, interquartile range, minimum/maximum, and standard deviations were calculated for continuous variables, including the HRQOL outcomes. Due to small sample size (22), the skewness of the outcomes (FACT-MM, FACT-G, TOI) were analyzed, and it was determined that all outcomes were left-skewed. Due to the left-skewed distribution, non-parametric methods were employed for comparative analyses. To assess associations between each of the continuous outcomes and the covariates, Mann-Whitney U and Kruskal-Wallis tests, were run, as appropriate based on number of levels, using univariate modeling. For dichotomized outcomes, Fisher's exact tests were utilized where appropriate. The sample size limited analysis to univariate procedures. Missing data was limited to only 4 subjects with unknown R-ISS stages. This was accounted for in analyses that used R-ISS by excluding those subjects for those specific analyses. All analyses were conducted using SAS 9.4.

## Results

*Patient Characteristics*

Between December 2021 and July 2022, 22 patients, treated at Winship Cancer Institute of Emory University, were enrolled in the study. FACT-MM questionnaire was completed on day of enrollment. Subjects had a median time from diagnosis to enrollment of 6.5 years and time from CAR-T infusion to enrollment ranged from 57 – 938 days (median: 246.5). Median age of participants was 64 years (range: 43-86 years), slightly lower than the average age at diagnosis for myeloma. Men made up 54.55% of the sample, and 54.55% of the sample were white (Table 1). The majority of patients were standard risk (59.09%), R-ISS stage III (45.45%) and had achieved a complete response (CR) or stringent complete response (sCR) per International Myeloma Working Group (IMWG) criteria post-CAR-T (63.64%). Most of the subjects had a documented history of osseous lesions (68.18%), while 22.73% had documented extramedullary disease. Post CAR-T CRS was documented in 86.36% of subjects. Subjects had undergone a median of 4 prior anti-myeloma therapies. **Table 1** provides further breakdown of subject demographics, disease characteristics, and comorbidities.

*HRQOL outcomes*

Overall HRQOL measurements during study period were relatively high with median FACT-MM of 137.5 out of possible 164 points, median FACT-G of 93 out of 108, median TOI of 95 out of 112 possible points. The high scores were also found in the subscores with median PWB and SWB of 26 out of 28, EWB median of 21 out of 24 and FWB median of 22 out of 28 possible points. There were no statistically significant differences observed in any of the outcomes, both continuous and dichotomous, between sexes or age groups. The analysis did yield one statistically significant difference among races, for the TOI outcome when TOI was dichotomized on the median of 95 points. Summary of medians and IQRs for all outcomes are in

**Table 2**. Visualizations of the comparisons and respective p-values for all covariates and outcomes are also included in the tables and figures section.

*Disease characteristics and comorbidities*

Myeloma disease characteristics were also not found to be associated with any differences in the target outcomes among the sample population. R-ISS stage, cytogenetic risk stratification, years since diagnosis, and history of either extramedullary disease or bone lesions were all analyzed, therefore it was not possible to reject the null hypothesis of no difference between groups with any of them. As MM is a disease that often has a heavy symptom burden, the analysis also explored associations with common comorbidities, as well as the Charlson Comorbidity Index (CCI) measurements and the HRQOL outcomes of interest. History of hypertension resulted in a statistically significant difference in PWB measurements when dichotomized on the median value of the sample. Subjects with a history of Gilbert's syndrome had a statistically significant difference in FACT-MM (p-value: 0.03), FACT-G (p-value: 0.03), pain (p-value: 0.04), PWB (p-value: 0.03), and FWB (p-value: 0.01). Charlson Comorbidity Index measurements were grouped by scores of 0 and scores between 2 and 4. There were no statistically significant differences in the HRQOL outcomes of interest between the two groups. History of renal or cardiac impairment, and type 2 diabetes mellitus also did not yield any statistically significant differences among the outcomes.

*Treatment history associations*

Prior lines of therapy were associated with some statistically significant differences in outcomes. TOI (p-value: 0.05), myeloma (p-value: 0.04), and pain subscales, measured on a continuous scale, were significantly different between subjects who had less than or equal to 4, and greater than 4 prior lines of therapy. These differences remained when dichotomizing the

outcomes on the median scores for both the myeloma (p-value: 0.03) and pain (p-value: 0.01) subscales. Prior types of therapy were also associated with some significant differences. Lenalidomide exposure was not associated with statistically significant differences in any of the outcomes. However, prior exposure to daratumumab and carfilzomib were associated with statistically significant differences in myeloma (p-values: 0.05) and pain subscores (p-values: 0.01) when measured on a continuous scale. These differences remained when dichotomizing the outcomes for myeloma (p-values: 0.02) and pain (p-values: 0.03) subscores. Prior carfilzomib exposure status was associated with differences in TOI (p-value: 0.01), FACT-G (p-value: 0.04), myeloma (p-value: 0.01) and pain (p-value: 0.03) subscores, and PWB (p-value: 0.02) on a continuous scale. Differences in these outcomes remained when dichotomizing the TOI (p-value: 0.03), myeloma (p-value: 0.01), and pain (p-value: 0.03) subscores on the median values of the sample.

Though statistically significant differences were not seen in FACT-MM for any of the treatment exposures, or the prior lines of therapies, there were marked differences in medians and IQRs among the groups. For example, the median FACT-MM for the heavily pre-treated subjects (>4 prior lines of therapy) was 135 (IQR: 9.5), while the non-heavily pre-treated group median was higher, at 142 (IQR: 21). Similarly, there were differences of 9.5 – 10 between the median FACT-MM scores in the exposed vs. non-exposed groups for pomalidomide (exposed median: 135, non-exposed median: 145), daratumumab (exposed median: 135, non-exposed median: 145), and carfilzomib (exposed median: 135.5, non-exposed median: 145). Complete comparisons can be found in **Table 3**.

*CAR-T specific covariates*

Predictors related to CAR-T treatment itself were also analyzed. Time since CAR-T infusion, IMWG best response, CRS, and neurotoxicity diagnoses, as well as the addition of maintenance therapy to keep subjects in a desired disease response state, were all analyzed for differences in HRQOL outcomes. None of the CAR-T specific covariate analyses resulted in statistically significant differences, with similar medians and IQRs as well, as summarized in **Table 3**.

## Discussion

This is the first study that assessed the late effects of CAR-T therapy on health-related quality of life in real-world relapsed/refractory multiple myeloma patients who achieved a favorable disease response at Winship Cancer Institute of Emory University. Findings suggest that individuals in this patient population had overall high patient-reported HRQOL outcomes following the acute period after CAR-T infusion. Previously published HRQOL data on RRMM CAR-T patients was derived from clinical trial findings. This study sample was comprised of patients who had undergone CAR-T in both clinical trial and commercial settings.

As both a clinician and a researcher, I have worked with RRMM patients for a number of years and have had the opportunity to learn how patients and caretakers may have different definitions of goals for disease and treatment outcomes, aside from the standard clinical outcomes that clinicians use to measure disease response. Patients may value maintaining social, emotional, and functional well-being in addition to physical well-being. For those individuals, having data that can provide insight into what they may expect from different treatment options is imperative. The lack of available data in this realm was the foundation for the development of

the study's main objective; to assess the impact of CAR-T therapy, and potential predictors, on HRQOL in the RRMM patient population.

The results from this study give clinicians examples of HRQOL outcomes that can be used to discuss risks and benefits of CAR-T based on patient characteristics. One specific example is with patient age; as the results did not find any statistically significant differences in HRQOL outcomes between subjects 69 years or less, and those aged 70 years and above. The average age at diagnosis of multiple myeloma is 69 years old, but standard of care treatment recommendations change for individuals over the age of 65 (Grant et al., 2021;National Cancer Institute, 2022). Despite making up a substantial portion of the myeloma patient population, older adults may be excluded from clinical trials, and clinicians may be hesitant to utilize novel therapy approaches due to concerns over increased toxicities, comorbidities, and frailty. (Dempsey et al., 2019; Wildes, 2017). The lack of differences between age groups, gives evidence that older adult patients may receive the same HRQOL benefits as their younger counterparts. This is similar to findings in recent years that have found that clinical benefits for autologous stem cell transplantation (ASCT) carry into older adults with myeloma who have previously been less likely to be offered ASCT (Joseph et al., 2021). While hypertension and Gilbert's syndrome were associated with differences in HRQOL outcomes, differences in Charlson Comorbidity Index scores, which is intended to predict long-term mortality, were not associated with differences in HRQOL (Charlson et al., 2022). These results suggest that a heavy symptom burden and comorbidities do not necessarily translate to poorer HRQOL outcomes in CAR-T patients, but further analysis is warranted, with a larger sample. Similarly, there were no significant differences observed in comparisons of R-ISS disease stages, cytogenetic risk stratification, and history of EMD or bone lesions. These findings suggest that high-risk disease

characteristics should not be a limiting factor in decision making for CAR-T treatment when maintaining HRQOL is a priority.

Presently, CAR-T is only FDA approved for heavily pre-treated individuals (4 or more prior lines of therapy), but this dataset included individuals with as few as 1 and as many as 9 prior lines (Rajkumar, 2022). Subjects were categorized as either less than 4, or at least 4 prior lines of therapy for analysis. Statistically significant differences were found among TOI, myeloma, and pain subscores. Additional analysis, with a larger sample, would be necessary to interpret these differences further. Prior exposures to specific drug classes were associated with some differences in the outcome as well. Significant differences were found as reported in the results section, when comparing exposure status of both daratumumab and carfilzomib. However, it is important to note that these drugs are approved for use in heavily pre-treated patients, so there may be some correlation attributed to the number of prior lines as well (Rajkumar, 2022).

Cytokine release syndrome and neurotoxicity are commonly reported adverse events associated with CAR-T infusion; onset of CRS is typically within the first 14 days of infusion, while neurotoxicity may manifest past the initial month post-infusion (Brudno & Kochenderfer, 2019; Cohen et al., 2022). These diagnoses are typically reversible, but the physical manifestations, including fever, hypotension, cognitive and personality changes, may be frightening to individuals who are considering CAR-T therapy. While the majority of subjects (86.36%) experienced at least grade 1 CRS, and 27.28% experienced at least grade 1 neurotoxicity, there was no statistically significant differences in HRQOL outcomes between groups who had been diagnosed with CRS or neurotoxicity prior to study enrollment, and those

who did not. This indicates that any HRQOL impairment that may have come from CRS or neurotoxicity, has likely corrected itself past 2 months post-treatment.

Notable limitations do arise from this study and analysis. First, and most influential, is the small sample size of 22. This sample size was based on feasibility of collecting an attainable sample size within a fixed time frame for the purpose of fulfilling requirements of a graduate program. Due to the small size, results from this sample may not be generalizable outside of the study population. Another limitation is the cross-sectional design of the study. The results reflect patient-reported outcomes but are only representative of the past 7 days prior to the survey date. FACT-MM, and other patient-reported HRQOL measurement tools, are equipped to be used in longitudinal analyses as well. Where the current dataset found that time since infusion does not result in HRQOL differences in patients who are at least 2 months out, longitudinal data could be used to strengthen this finding, as well as potentially identify time points where HRQOL does change from pre-treatment baseline. I recommend that future, expanded studies enroll subjects prior to CAR-T infusion, administer baseline FACT-MM survey, and repeat at timepoints through and after treatment.

## Conclusion

CAR-T is a novel adaptive cellular therapy which has shown clinical promise in RRMM patient population. The results obtained from the analyses of this pilot study show that there is much to still be learned about factors that affect HRQOL in patients who have received CAR-T therapy for treatment of myeloma, who have not experienced disease progression. Subjects had similar scores in the overall FACT-MM assessment, as well as the subscores including myeloma specific symptoms, pain, and well-being, regardless of patient demographics, disease characteristics and some comorbidities that are common to this patient population. These

findings are suggestive of an overall positive effect on HRQOL from CAR-T therapy, to correlate with positive clinical outcomes that have been previously reported by clinical trial data. Due to the limitations of this pilot study, it is recommended that HRQOL continue to be studied in the setting of multiple myeloma CAR-T patients with a larger, more heterogenous sample, as well as potential longitudinal analyses. The findings from this study and potential future iterations and expanded studies may allow patients, caregivers, and clinicians alike to navigate multifactorial, individualized treatment planning.

## Tables and figures

**Table 1**
**Descriptive statistics of sample**

| | n | Median (range) or % |
|---|---|---|
| *Demographics* | | |
| **Sex** | | |
| Male | 12 | 54.55 |
| Female | 10 | 45.45 |
| **Age** | | |
| Median (range) yrs. | | 64 (43-86) |
| Distribution (yrs.) | | |
| 18-69 | 18 | 81.82 |
| 70+ | 4 | 18.12 |
| **Race** | | |
| White | 12 | 54.55 |
| Black or African American | 8 | 36.36 |
| Asian | 2 | 9.09 |
| **Ethnicity** | | |
| Non-Hispanic or Latinx | 22 | 100 |
| *Baseline Disease Characteristics* | | |
| **R-ISS stage** | | |
| 1 | 3 | 13.64 |
| 2 | 6 | 27.27 |
| 3 | 10 | 45.45 |
| unknown | 3 | 13.64 |
| **Risk stratification** | | |
| Standard | 13 | 59.09 |
| High | 9 | 40.91 |
| **Years since myeloma diagnosis** | | 6.50 (3-17) |
| **Prior lines of therapy** | | 4 (1-9) |
| **Prior treatment exposures** | | |
| ASCT | 22 | 100 |

| | | |
|---|---|---|
| lenalidomide | 21 | 95.45 |
| pomalidomide | 18 | 81.82 |
| bortezomib | 22 | 100 |
| carfilzomib | 12 | 54.55 |
| daratumumab | 18 | 81.82 |
| **Bone lesions** | 15 | 68.18 |
| **Extramedullary disease** | 5 | 22.73 |
| **Days since CAR-T infusion** | | 246.50 (57-938) |
| *Medical History* | | |
| **Hypertension** | 16 | 72.73 |
| **Renal disease** | 2 | 9.09 |
| **Diabetes mellitus type 2** | 3 | 13.64 |
| **Hepatic Impairment** | 2 | 9.09 |
| **Cardiac Impairment** | 5 | 22.73 |
| **CCI** | | 0.5 (0-4) |
| *Post CAR-T characteristics* | | |
| **CRS** | | |
| None | 3 | 13.64 |
| Grade 1 | 14 | 63.64 |
| Grade 2 | 4 | 18.18 |
| Grade 3 | 1 | 4.55 |
| **Neurotoxicity** | | |
| None | 16 | 72.73 |
| Grade 1 | 5 | 22.73 |
| Grade 2 | 1 | 4.55 |
| **Best Response (IMWG)** | | |
| **PR** | 1 | 4.55 |
| **VGPR** | 7 | 31.82 |
| **CR** | 3 | 13.64 |
| **sCR** | 11 | 50 |

| | | |
|---|---|---|
| **Maintenance therapy** | 1 | 4.55 |

**Table 2**
**Descriptive statistics of outcomes**

| Outcome *(poss. score values)* | Median (IQR) |
|---|---|
| **FACT-MM** *(0-164)* | 137.5 (18.5) |
| **Trial Outcome Index (TOI)** *(0-112)* | 95 (17) |
| **FACT-G** *(0-108)* | 93 (10.5) |
| **Myeloma subscale** *(0-56)* | 46 (9) |
| **Pain subscale** *(0-16)* | 12 (4) |
| **Physical well-being (PWB)** *(0-28)* | 26 (5) |
| **Emotional well-being (EWB)** *(0-24)* | 21 (3) |
| **Social well-being (SWB)** *(0-28)* | 26 (4) |
| **Functional well-being (FWB)** *(0-28)* | 22 (4) |

**Table 3 Charlson Comorbidity by HRQOL Outcome**

| CCI by outcome | Median (IQR) | | p-value |
|---|---|---|---|
| **FACT-MM** | | 138 | 0.79 |
| 0 | (21) | 137 | |
| 1-4 | | (18.5) | |
| **TOI** | | 98 | 0.24 |
| 0 | (16) | 88 (18) | |
| 1-4 | | | |
| **FACT-G** | | 91 | 0.95 |
| 0 | (27) | 93(10.5) | |
| 1 | | | |
| **MYELOMA** | | 48 | 0.36 |
| 0 | (10) | 44 (13) | |
| 1 | | | |
| **PAIN** | | 12 | >0.99 |
| 0 | (5) | 12 (4) | |
| 1 | | | |

**Table 4 FACT-MM Median by variables**

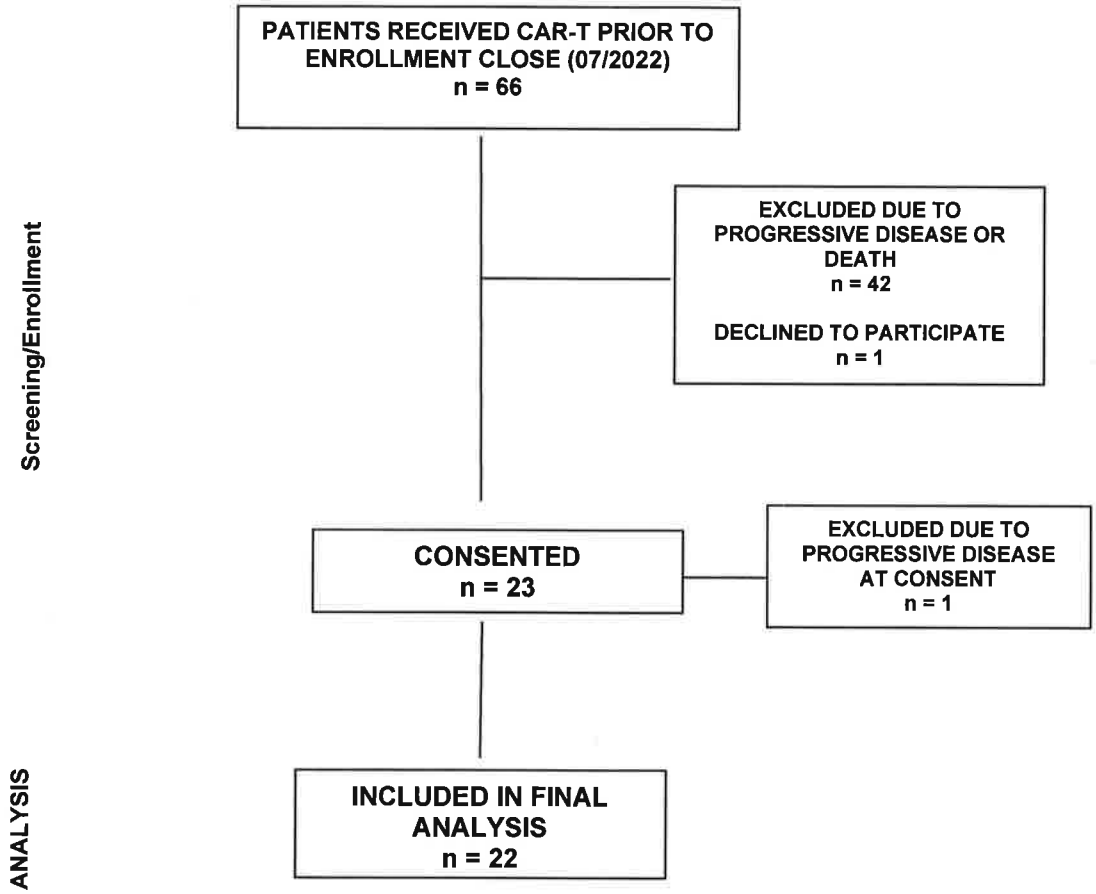
| Variable | Median (IQR) | p-value |
|---|---|---|
| **Sex** | 137 (30.25) | 0.97 |
| Male | 139.5 (16) | |
| Female | | |
| **Age** | | 0.89 |
| Distribution (yrs.) | | |
| 18-69 | 137.5 (18.5) | |
| 70+ | 138.5 (35.5) | |
| **Race** | 135.5 (32.5) | 0.25* |
| White | 144 (15) | |
| Black or African American | 145.9 (3.8) | |
| Asian | | |

| Variable | Median (IQR) | p-value |
|---|---|---|
| **R-ISS stage** | | 0.90 |
| < 3 | 137.5 (13.4) | |
| 3 | 138.5 (37) | |
| **Risk stratification** | | 0.16 |
| Standard | 144 (18) | |
| High | 136 (11) | |
| **Years since myeloma diagnosis** | | 0.65 |
| ≤ 6.5 | 136 (36) | |
| > 6.5 | 138 (17.8) | |
| **Prior lines of therapy** | | 0.24 |
| ≤ 4 | 142 (21) | |
| > 4 | 135 (9.5) | |
| **Bone lesions Hx.** | | 0.62 |
| No | 138 (17) | |
| Yes | 137 (19.5) | |
| **Extramedullary disease Hx.** | | 0.39 |
| No | 138 (11) | |
| Yes | 128.5 (37) | |
| **Days since CAR-T infusion** | | 0.20 |
| ≤ 246.5 | 135 (15) | |
| > 246.5 | 144 (18) | |

**Table 4 cont.**

| Variable | Median (IQR) | p-value |
|---|---|---|
| **Cytokine Release Syndrome** | | 0.57 |
| None | 136 (7) | |
| Grade 1-3 | 142 (20.8) | |
| **Neurotoxicity** | | 0.68 |
| None | 137.5 (18.3) | |
| Grade 1 or 2 | 138.5(19) | |
| **Best Response (IMWG)** | | 0.88 |
| < Complete Response | 140.5 (19.7) | |
| ≥ Complete Response | 137.5 (14) | |

**CONSORT FLOW DIAGRAM**



***p-values for all comparisons: outcomes x variables of interest***

| **Sex** | |
|---|---|
| | **p-values** |
| **CONTINOUS OUTCOMES** | |
| FACT-MM | 0.97 |
| TOI | 0.67 |
| FACT-G | 0.95 |
| Myeloma | 0.47 |
| Pain | 0.18 |
| PWB | 0.10 |
| EWB | 0.95 |
| SWB | 0.23 |
| FWB | 0.49 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | 0.67 |
| FACT-G | >0.99 |
| Myeloma | >0.99 |
| Pain | 0.67 |
| PWB | 0.35 |
| EWB | 0.69 |
| SWB | 0.38 |
| FWB | 0.42 |

| **Race** | |
|---|---|
| | **p-values** |
| **CONTINOUS OUTCOMES** | |
| FACT-MM | 0.25 |
| TOI | 0.06 |
| FACT-G | 0.55 |
| Myeloma | 0.07 |
| Pain | 0.06 |
| PWB | 0.10 |
| EWB | 0.50 |
| SWB | 0.72 |
| FWB | 0.19 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.26 |
| TOI | **0.04** |
| FACT-G | 0.21 |
| Myeloma | 0.07 |
| Pain | 0.11 |
| PWB | 0.38 |
| EWB | 0.48 |
| SWB | 0.83 |
| FWB | 0.25 |

| **Age ($\leq 69$ *vs.* $\geq 70$)** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.89 |
| TOI | 0.64 |
| FACT-G | 0.76 |
| Myeloma | 0.69 |
| Pain | 0.69 |
| PWB | 0.26 |
| EWB | 0.89 |
| SWB | 0.95 |
| FWB | 0.85 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | >0.99 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | 0.54 |
| EWB | >0.99 |
| SWB | 0.60 |
| FWB | >0.99 |

| **Years since diagnosis** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.65 |
| TOI | 0.69 |
| FACT-G | 0.29 |
| Myeloma | 0.84 |
| Pain | 0.95 |
| PWB | 0.26 |
| EWB | 0.11 |
| SWB | 0.42 |
| FWB | 0.77 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | 0.67 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | 0.64 |
| EWB | 0.67 |
| SWB | 0.66 |
| FWB | 0.39 |

| **Lines of therapy dichotomous** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.24 |
| TOI | **0.05** |
| FACT-G | 0.88 |
| Myeloma | **0.04** |
| Pain | **0.05** |
| PWB | 0.56 |
| EWB | 0.48 |
| SWB | 0.22 |
| FWB | 0.24 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.08 |
| TOI | 0.08 |
| FACT-G | 0.19 |
| Myeloma | **0.03** |
| Pain | **0.01** |
| PWB | 0.18 |
| EWB | 0.42 |
| SWB | 0.66 |
| FWB | >0.99 |

| **Prior lenalidomide exposure** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.36 |
| TOI | 0.68 |
| FACT-G | 0.46 |
| Myeloma | 0.77 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | 0.23 |
| SWB | 0.82 |
| FWB | 0.55 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | 0.45 |
| Myeloma | 0.46 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | 0.46 |
| SWB | >0.99 |
| FWB | 0.41 |

| **Prior pomalidomide exposure** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.08 |
| TOI | 0.67 |
| FACT-G | 0.95 |
| Myeloma | **0.05** |
| Pain | **0.01** |
| PWB | 0.10 |
| EWB | >0.99 |
| SWB | 0.48 |
| FWB | 0.25 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.09 |
| TOI | 0.09 |
| FACT-G | 0.55 |
| Myeloma | **0.03** |
| Pain | **0.02** |
| PWB | 0.29 |
| EWB | >0.99 |
| SWB | 0.60 |
| FWB | >0.99 |

| **Prior daratumumab exposure** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.08 |
| TOI | 0.07 |
| FACT-G | 0.29 |
| Myeloma | **0.05** |
| Pain | **0.01** |
| PWB | 0.10 |
| EWB | >0.99 |
| SWB | 0.48 |
| FWB | 0.25 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.09 |
| TOI | 0.09 |
| FACT-G | 0.29 |
| Myeloma | **0.03** |
| Pain | **0.02** |
| PWB | 0.29 |
| EWB | >0.99 |
| SWB | 0.60 |
| FWB | >0.99 |

| **Prior carfilzomib exposure** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.09 |
| TOI | **0.01** |
| FACT-G | **0.04** |
| Myeloma | **0.01** |
| Pain | **0.03** |
| PWB | **0.02** |
| EWB | 0.44 |
| SWB | 0.61 |
| FWB | 0.14 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.20 |
| TOI | **0.03** |
| FACT-G | 0.39 |
| Myeloma | **0.01** |
| Pain | **0.03** |
| PWB | 0.06 |
| EWB | >0.99 |
| SWB | 0.68 |
| FWB | 0.67 |

| **Maintenance therapy** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.77 |
| TOI | 0.77 |
| FACT-G | 0.68 |
| Myeloma | >0.99 |
| Pain | 0.41 |
| PWB | 0.55 |
| EWB | 0.59 |
| SWB | 0.68 |
| FWB | 0.73 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | >0.99 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | 0.45 |
| SWB | >0.99 |
| FWB | >0.99 |

| R-ISS | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.90 |
| TOI | 0.90 |
| FACT-G | 0.88 |
| Myeloma | 0.99 |
| Pain | 0.93 |
| PWB | 0.65 |
| EWB | 0.65 |
| SWB | 0.42 |
| FWB | 0.67 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.70 |
| TOI | 0.58 |
| FACT-G | 0.39 |
| Myeloma | 0.70 |
| Pain | 0.68 |
| PWB | 0.64 |
| EWB | >0.99 |
| SWB | >0.99 |
| FWB | 0.33 |

| ISS Dichotomous | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.67 |
| TOI | >0.99 |
| FACT-G | 0.51 |
| Myeloma | >0.99 |
| Pain | 0.95 |
| PWB | 0.84 |
| EWB | 0.89 |
| SWB | 0.25 |
| FWB | >0.99 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | 0.67 |
| FACT-G | 0.69 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | >0.99 |
| SWB | 0.68 |
| FWB | 0.67 |

| **Risk stratification** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.16 |
| TOI | 0.61 |
| FACT-G | 0.10 |
| Myeloma | 0.73 |
| Pain | 0.99 |
| PWB | 0.29 |
| EWB | 0.08 |
| SWB | 0.48 |
| FWB | 0.61 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.39 |
| TOI | 0.39 |
| FACT-G | 0.10 |
| Myeloma | 0.42 |
| Pain | 0.67 |
| PWB | 0.33 |
| EWB | 0.10 |
| SWB | >0.99 |
| FWB | 0.67 |

| **Extramedullary Disease Hx** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.39 |
| TOI | 0.13 |
| FACT-G | 0.51 |
| Myeloma | 0.73 |
| Pain | 0.31 |
| PWB | 0.55 |
| EWB | 0.84 |
| SWB | >0.99 |
| FWB | 0.29 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | >0.99 |
| Myeloma | 0.32 |
| Pain | 0.36 |
| PWB | 0.59 |
| EWB | >0.99 |
| SWB | >0.99 |
| FWB | 0.36 |

| **Bone lesions Hx.** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.62 |
| TOI | 0.69 |
| FACT-G | 0.85 |
| Myeloma | 0.77 |
| Pain | 0.50 |
| PWB | 0.96 |
| EWB | 0.69 |
| SWB | 0.61 |
| FWB | 0.52 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | 0.65 |
| Myeloma | 0.65 |
| Pain | 0.38 |
| PWB | 0.62 |
| EWB | >0.99 |
| SWB | >0.99 |
| FWB | 0.38 |

| **Hypertension** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.12 |
| TOI | 0.68 |
| FACT-G | 0.21 |
| Myeloma | 0.70 |
| Pain | 0.76 |
| PWB | 0.16 |
| EWB | 0.12 |
| SWB | 0.15 |
| FWB | >0.99 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.15 |
| TOI | 0.64 |
| FACT-G | 0.35 |
| Myeloma | >0.99 |
| Pain | 0.66 |
| PWB | **0.03** |
| EWB | 0.35 |
| SWB | 0.14 |
| FWB | 0.66 |

| Renal Impairment | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.71 |
| TOI | 0.61 |
| FACT-G | 0.56 |
| Myeloma | 0.89 |
| Pain | 0.70 |
| PWB | 0.16 |
| EWB | 0.46 |
| SWB | 0.30 |
| FWB | 0.67 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | 0.48 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | 0.20 |
| SWB | 0.52 |
| FWB | >0.99 |

| Type 2 Diabetes Mellitus | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.35 |
| TOI | 0.32 |
| FACT-G | 0.23 |
| Myeloma | 0.60 |
| Pain | >0.99 |
| PWB | 0.65 |
| EWB | 0.06 |
| SWB | 0.94 |
| FWB | 0.13 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.37 |
| TOI | >0.99 |
| FACT-G | >0.99 |
| Myeloma | >0.99 |
| Pain | >0.99 |
| PWB | 0.53 |
| EWB | 0.22 |
| SWB | >0.99 |
| FWB | 0.24 |

| **Hepatic Impairment** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | **0.03** |
| TOI | 0.06 |
| FACT-G | **0.03** |
| Myeloma | 0.08 |
| Pain | **0.04** |
| PWB | **0.03** |
| EWB | 0.36 |
| SWB | 0.46 |
| FWB | **0.01** |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.48 |
| TOI | 0.48 |
| FACT-G | 0.48 |
| Myeloma | 0.48 |
| Pain | 0.49 |
| PWB | >0.99 |
| EWB | >0.99 |
| SWB | 0.52 |
| FWB | 0.49 |

| **Cardiac Impairment** | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.66 |
| TOI | 0.41 |
| FACT-G | 0.92 |
| Myeloma | 0.41 |
| Pain | 0.27 |
| PWB | 0.39 |
| EWB | 0.37 |
| SWB | 0.53 |
| FWB | 0.63 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | 0.31 |
| TOI | 0.31 |
| FACT-G | >0.99 |
| Myeloma | 0.32 |
| Pain | 0.36 |
| PWB | 0.27 |
| EWB | 0.32 |
| SWB | 0.31 |
| FWB | 0.36 |

| Charlson Comorbidity Index | |
|---|---|
| | p-values |
| CONTINUOUS OUTCOMES | |
| FACT-MM | 0.79 |
| TOI | 0.24 |
| FACT-G | 0.95 |
| Myeloma | 0.36 |
| Pain | >0.99 |
| PWB | 0.58 |
| EWB | 0.63 |
| SWB | 0.42 |
| FWB | 0.32 |
| | |
| DICHOTOMOUS OUTCOMES | |
| FACT-MM | >0.99 |
| TOI | >0.99 |
| FACT-G | >0.99 |
| Myeloma | 0.67 |
| Pain | >0.99 |
| PWB | >0.99 |
| EWB | >0.99 |
| SWB | 0.66 |
| FWB | 0.39 |

| Cytokine Release Syndrome | |
|---|---|
| | p-values |
| CONTINUOUS OUTCOMES | |
| FACT-MM | 0.57 |
| TOI | 0.48 |
| FACT-G | 0.57 |
| Myeloma | 0.50 |
| Pain | 0.92 |
| PWB | >0.99 |
| EWB | 0.26 |
| SWB | 0.75 |
| FWB | 0.32 |
| | |
| DICHOTOMOUS OUTCOMES | |
| FACT-MM | 0.21 |
| TOI | 0.21 |
| FACT-G | 0.22 |
| Myeloma | 0.22 |
| Pain | 0.24 |
| PWB | 0.53 |
| EWB | 0.22 |
| SWB | >0.99 |
| FWB | 0.24 |

| Neurotoxicity | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.68 |
| TOI | 0.27 |
| FACT-G | 0.59 |
| Myeloma | 0.24 |
| Pain | 0.35 |
| PWB | 0.33 |
| EWB | 0.80 |
| SWB | 0.23 |
| FWB | 0.71 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | 0.64 |
| FACT-G | 0.80 |
| Myeloma | 0.45 |
| Pain | 0.20 |
| PWB | 0.46 |
| EWB | >0.99 |
| SWB | 0.57 |
| FWB | 0.32 |

| Neurotoxicity Y/N | |
|---|---|
| | **p-values** |
| **CONTINUOUS OUTCOMES** | |
| FACT-MM | 0.68 |
| TOI | 0.55 |
| FACT-G | 0.71 |
| Myeloma | 0.42 |
| Pain | 0.22 |
| PWB | 0.41 |
| EWB | 0.48 |
| SWB | 0.62 |
| FWB | 0.99 |
| | |
| **DICHOTOMOUS OUTCOMES** | |
| FACT-MM | >0.99 |
| TOI | 0.64 |
| FACT-G | >0.99 |
| Myeloma | 0.35 |
| Pain | 0.18 |
| PWB | >0.99 |
| EWB | 0.65 |
| SWB | 0.62 |
| FWB | >0.99 |

| BEST RESPONSE | |
|---|---|
| | p-values |
| CONTINUOUS OUTCOMES | |
| FACT-MM | 0.88 |
| TOI | 0.63 |
| FACT-G | 0.60 |
| Myeloma | 0.41 |
| Pain | 0.75 |
| PWB | 0.58 |
| EWB | 0.63 |
| SWB | 0.14 |
| FWB | 0.80 |
| | |
| DICHOTOMOUS OUTCOMES | |
| FACT-MM | >0.99 |
| TOI | 0.66 |
| FACT-G | 0.38 |
| Myeloma | >0.99 |
| Pain | 0.66 |
| PWB | 0.62 |
| EWB | >0.99 |
| SWB | 0.08 |
| FWB | >0.99 |

| Days since CAR-T | |
|---|---|
| | p-values |
| CONTINUOUS OUTCOMES | |
| FACT-MM | 0.20 |
| TOI | 0.41 |
| FACT-G | 0.51 |
| Myeloma | 0.47 |
| Pain | 0.15 |
| PWB | 0.18 |
| EWB | 0.84 |
| SWB | 0.71 |
| FWB | >0.99 |
| | |
| DICHOTOMOUS OUTCOMES | |
| FACT-MM | 0.40 |
| TOI | 0.40 |
| FACT-G | 0.67 |
| Myeloma | 0.20 |
| Pain | 0.39 |
| PWB | 0.64 |
| EWB | 0.67 |
| SWB | >0.99 |
| FWB | >0.99 |

## Chapter 3: Future Direction/ Public Health Implications

This is the first study to assess the late effects of CAR-T therapy on quality of life in real-world relapsed/refractory multiple myeloma patients who achieved a favorable disease response at Winship Cancer Institute of Emory University Hospital. Overall findings suggest that individuals in this patient population had a favorable HRQOL outcomes relative to the FACT-MM scale, following the acute period after CAR-T infusion. The results from this study give clinicians examples of HRQOL outcomes that can be used to discuss risks and benefits of CAR-T based on patient characteristics. Previously published HRQOL data on RRMM CAR-T patients has been limited to clinical trial subjects due to the fact that the first products, idecabtagene vicleucel and Ciltacabtagene autoleucel have only recently been granted FDA approval. This study however, included subjects who had undergone CAR-T in trial and commercial settings, potentially diversifying the population that findings may be generalized to.

As both a clinician and a researcher, I have worked with RRMM patients for a number of years and have had the opportunity to learn how patients and caretakers may have different definitions of goals for disease and treatment outcomes, aside from the standard clinical outcomes that clinicians use to measure disease response. Patients may value maintaining social, emotional, and functional well-being in addition to physical well-being. For those individuals, having data that can provide insight into what they may expect from different treatment options is imperative. The lack of available data in this realm was the foundation for the development of the study's main objective; to assess the impact of CAR-T therapy, and potential predictors, on HRQOL in the RRMM patient population.

The field of RRMM research has seen exponential growth in recent decades, but focus remains heavily focused on development of a curative treatment option. As novel therapies bring increased PFS intervals and OS rates, many patients and clinicians have begun to explore how these treatments are able to balance duration of response with quality of life; to include physical, psychosocial, spiritual, and functional dimensions. Though there is a desire for and benefit from HRQOL data, there are still scarce myeloma clinical trials that use HRQOL measurements as an endpoint. The United States Department of Health and Human Services' Office of Disease Prevention and Health Promotion (ODPHP) has identified increasing the mental and physical health-related quality of life of cancer survivors as a research objective for Healthy People 2030 (2022). Results from this study, and other oncology HRQOL studies, are important for the ODPHP to have available to determine if this research objective should be considered a core objective in the future. The recent increases in 5-year survival for multiple myeloma, along with the heavy symptom burden associated with the disease, provide reasoning for researching HRQOL and potential improvements in the patient population.

The average age at diagnosis of multiple myeloma is 69 years old, but standard of care treatment recommendations change for individuals over the age of 65 (Grant et al., 2021;National Cancer Institute, 2022). Despite making up a substantial portion of the myeloma patient population, older adults may be excluded from clinical trials, and clinicians may be hesitant to utilize novel therapy approaches due to concerns over increased toxicities, comorbidities, and frailty. (Dempsey et al., 2019; Wildes, 2017). The lack of differences between age groups, gives evidence that older adult patients may receive the same HRQOL benefits as their younger counterparts. This is similar to findings in recent years that have found that clinical benefits for autologous stem cell transplantation (ASCT) carry into older adults with myeloma

who have previously been less likely to be offered ASCT (Joseph et al., 2021). While hypertension and Gilbert's syndrome were associated with differences in HRQOL outcomes, differences in Charlson Comorbidity Index scores, which is intended to predict long-term mortality, were not associated with differences in HRQOL (Charlson et al., 2022). These results suggest that a heavy symptom burden and comorbidities do not necessarily translate to poorer HRQOL outcomes in CAR-T patients, but further analysis is warranted, with a larger sample. Similarly, there were no significant differences observed in comparisons of R-ISS disease stages, cytogenetic risk stratification, and history of EMD or bone lesions. These findings suggest that high-risk disease characteristics should not be a limiting factor in decision making for CAR-T treatment when maintaining HRQOL is a priority.

Presently, CAR-T is only FDA approved for heavily pre-treated individuals (4 or more prior lines of therapy), but this dataset included individuals with as few as 1 and as many as 9 prior lines (Rajkumar, 2022). Subjects were categorized as either less than 4, or at least 4 prior lines of therapy for analysis. Statistically significant differences were found among TOI, myeloma, and pain subscores. Additional analysis, with a larger sample, would be necessary to interpret these differences further. Prior exposures to specific drug classes were associated with some differences in the outcome as well. Significant differences were found as reported in the results section, when comparing exposure status of both daratumumab and carfilzomib. However, it is important to note that these drugs are approved for use in heavily pre-treated patients, so there may be some correlation attributed to the number of prior lines as well (Rajkumar, 2022).

The limited sample size of 22 individuals limited the available options for statistical analysis. This sample size was based on feasibility of collecting an attainable sample size within

a fixed time frame for the purpose of fulfilling requirements of a graduate program. Due to the small size, results from this sample may or may not be generalizable outside of the study population. Another limitation is the cross-sectional design of the study. The results reflect patient-reported outcomes but are only representative of the past 7 days prior to the survey date. FACT-MM, and other patient-reported HRQOL measurement tools, are equipped to be used in longitudinal analyses as well. While the study successfully captured data at a single time-point in the post-CAR-T journey of the subjects, HRQOL may fluctuate across days, weeks, and months. Where the current dataset found that time since infusion does not result in HRQOL differences in patients who are at least 2 months out, longitudinal data could be used to strengthen this finding, as well as potentially identify time points where HRQOL does change from pre-treatment baseline. I recommend that future, expanded studies enroll subjects prior to CAR-T infusion, administer baseline FACT-MM survey, and repeat at timepoints through and after treatment. The combination of the wide range of days since infusion (57 – 938) and the small sample size may have skewed this finding. This may hold true with other covariables as well, whether statistically significant differences were found or not. I recommend that future, expanded studies enroll subjects prior to CAR-T infusion, administer baseline FACT-MM survey, and repeat at timepoints through and after treatment.

As a novel adaptive cellular therapy, CAR-T has shown clinical promise in RRMM patient population. The results obtained from the analyses of this pilot study show that there is much to still be learned about factors that affect HRQOL in patients who have received CAR-T therapy for treatment of myeloma, who have not experienced disease progression. Subjects had similar scores in the overall FACT-MM assessment, as well as the subscores including myeloma specific symptoms, pain, and well-being, regardless of patient demographics, disease

characteristics and some comorbidities that are common to this patient population. These findings are suggestive of an overall positive effect on HRQOL from CAR-T therapy, to correlate with positive clinical outcomes that have been previously reported by clinical trial data, though it is important to address the limitations before generalizing beyond the single-site patient population.

Due to the limitations of this pilot study, it is recommended that HRQOL continue to be studied in the setting of multiple myeloma CAR-T patients with a larger, more heterogenous sample, as well as potential longitudinal analyses. The research team from this pilot study will continue to investigate HRQOL in this patient population, with plans to amend the current study protocol in order to better represent the research needs. Results of the initial study will be used as a guide for identifying needs when submitting amendments to the Emory University Institutional Review Board. As previously mentioned, longitudinal analysis is an intended next step, which will allow the researchers to evaluate how HRQOL changes throughout the treatment process. The findings from this study and potential future iterations and expanded studies may allow patients, caregivers, and clinicians alike to navigate multifactorial, individualized treatment planning.

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