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Maira A. Castaneda-Avila  
*University of Massachusetts Medical School*

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**THE ROLE OF A MONOCLONAL GAMMOPATHY OF UNDETERMINED  
SIGNIFICANCE DIAGNOSIS IN HEALTHCARE UTILIZATION**

A Dissertation Presented

By

MAIRA ALEJANDRA CASTAÑEDA-AVILA

Submitted to the Faculty of the  
University of Massachusetts Graduate School of Biomedical Science, Worcester  
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

MAY 13, 2021

CLINICAL AND POPULATION HEALTH RESEARCH

**THE ROLE OF A MONOCLONAL GAMMOPATHY OF UNDETERMINED  
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May 13, 2021

## **DEDICATION**

I dedicate this work to my lovely God, who had guide me and gave me the best parents, siblings, mentors, and friends that made possible for me to achieve this goal. I also dedicate this work to Martha L. Avila Carvajal my amazing mom who have made the most incredible sacrifices to offer me the best opportunities.

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## **ABSTRACT**

### **Background**

Monoclonal Gammopathy of Undetermined Significance (MGUS) is an understudied precursor of multiple myeloma (MM), the second most prevalent hematologic malignancy in the United States. This dissertation was designed to: (1) Describe the trajectories of serum biomarkers over time in patients with an MGUS diagnosis, (2) Determine if an MGUS diagnosis is associated with changes in healthcare service utilization, and (3) explore the patient- and provider-level drivers of healthcare utilization in patients with MGUS.

### **Methods**

Data sources include health claims and electronic health records from a community-based population of patients seeking care in central Massachusetts and primary qualitative data collected from providers and patients' interviews. The analyses included descriptive statistics, group-based trajectory modeling, conditional Poisson regression, and qualitative data analyses.

### **Results**



## ABSTRACT

(1) Three distinct multi-trajectory groups of creatinine and hemoglobin were identified. (2) The rates of emergency room, hospital, and outpatient visits were higher for patients with MGUS than patients without MGUS. (3) Patients have a basic understanding of MGUS; however, some patients feel anxiety, which may affect other aspects of their lives. Patients primarily see hematologists for follow-up care; other providers have less knowledge about MGUS.

### **Conclusions**

Biomarker trajectories characterize specific subpopulations of patients with MGUS over time. We found that an MGUS diagnosis is associated with higher healthcare utilization, especially during the months surrounding the diagnosis date. Finally, our study suggests that some patients with MGUS may need psychosocial support services and identifies a gap in knowledge around caring for MGUS patients among primary care providers.

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## LIST OF ABBREVIATIONS

ACRONYM	MEANING
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MGUS	Monoclonal gammopathy of undetermined significance
EHR	Electronic health records
Cr	Creatinine
Hgb	Hemoglobin
GBTM	Group-based trajectory modeling
ER	Emergency department/room

## PREFACE

The work presented in this dissertation has been previously presented and/or published (or is currently under review in a peer-review journal). See presentation and publication citations by chapter as of May 13, 2021 below.

### **Chapter II:** Multi-Trajectory Models of Serum Biomarkers among Patients with Monoclonal Gammopathy of Undetermined Significance

- Castañeda-Avila MA, Lapane KL, Pearson S, Zhou Y, Gurwitz J, Epstein MM (2020). Creatinine and Hemoglobin Multi-Trajectory Groups among Patients with Monoclonal Gammopathy of Undetermined Significance. InterLymph Annual Meeting (virtual)- Oral presentation
- Castañeda-Avila MA, Lapane KL, Pearson S, Zhou Y, Gurwitz J, Epstein MM (2021). Multi-trajectory models of multiple myeloma progression among patients with monoclonal gammopathy of undetermined significance. AACR annual meeting (virtual) – Poster presentation
- Castañeda-Avila MA, Lapane KL, Pearson S, Zhou Y, Gurwitz J, Epstein MM (2021). Multi-Trajectory Models of Serum Biomarkers among Patients with Monoclonal Gammopathy of Undetermined Significance. Under review

### **Chapter III:** Differences in Hospital, Emergency Room and Outpatient Visits Among Adults with and without Monoclonal Gammopathy of Undetermined Significance



## PREFACE

- Castañeda-Avila MA, Lapane KL, Pearson S, Zhou Y, Jesdale B, Epstein MM (2021). Emergency Room Utilization and Hospital Admissions among patients with Monoclonal Gammopathy of Undetermined Significance. Health Care Systems Research Network Conference (Virtual)- Poster presentation
- Manuscript in preparation for submission.

**Chapter IV:** Patient and provider-level drivers of healthcare utilization related to a diagnosis of Monoclonal Gammopathy of Undetermined Significance: A qualitative study

- Manuscript in preparation for submission

**CHAPTER I:**  
**INTRODUCTION**

## **CHAPTER I: INTRODUCTION**

### **EPIDEMIOLOGY OF MULTIPLE MYELOMA**

Multiple myeloma is the second most commonly diagnosed hematologic malignancy in the US.<sup>1-3</sup> In 2021, approximately 34,920 new cases of multiple myeloma, a malignancy of plasma cells, will be diagnosed, and nearly 12,410 deaths from multiple myeloma are expected to occur in the US.<sup>4-6</sup> Multiple myeloma is difficult to diagnose in early stages because it is usually asymptomatic.<sup>7</sup> In its more advanced stages, symptoms include anemia, bone fracture, calcium deficiencies, infections, and kidney dysfunction.<sup>7</sup> In the past decade, overall multiple myeloma survival rates have improved significantly. Patients diagnosed with this malignancy in the US had a 5-year survival rate of only 25-30% in the late 1970s,<sup>8</sup> whereas expected survival has doubled to 52.2% approximately 40 years later,<sup>9</sup> most likely due to the development and availability of effective therapies.<sup>10-13</sup> However, there is evidence of racial disparities in multiple myeloma incidence and mortality, and improvements in multiple myeloma survival have been differentially observed in racial/ethnic groups in the US.<sup>14</sup> Non-Hispanic White patients have experienced the greatest improvements in survival, followed by African-Americans, although the reasons for these disparities are not fully understood.<sup>15</sup> Differences in patterns of healthcare access and utilization may explain why non-Hispanic White patients experience better survival outcomes than patients of other races and ethnicities.<sup>16</sup>

## **OVERVIEW OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)**

Monoclonal Gammopathy of Undetermined Significance (MGUS) is an early pathogenic step in the development of multiple myeloma.<sup>17</sup> MGUS is a plasma cell disorder characterized by the overproduction of monoclonal protein.<sup>17</sup> MGUS is usually an asymptomatic condition incidentally diagnosed through blood tests.<sup>18</sup> The healthcare cost of MGUS follow-up in the US alone is likely to be more than \$100 million annually.<sup>19</sup> In the US, MGUS prevalence has been estimated at 2 to 3% among individuals 50 years and older and approximately 5% in persons 70 years and older, although most cases are undiagnosed.<sup>20</sup> Older adults, men, and people of African descent in the US are at higher risk of MGUS than respective comparison groups.<sup>21</sup> Each year, approximately 1% of patients with MGUS develop multiple myeloma;<sup>22</sup> however, few risk factors for progression are known, and the majority of patients live for many years without developing multiple myeloma.<sup>22</sup> Patients with MGUS are also at increased risk for developing other lymphoproliferative conditions including Waldenström macroglobulinemia, lymphoma, and amyloidosis.<sup>23</sup> Patients with MGUS do not undergo treatment until the disease progresses into multiple myeloma. However, patients with multiple myeloma who had a previous clinical MGUS diagnosis (median survival, 2.8 years) have better long-term survival than those without a prior diagnosis (median survival, 2.1 years).<sup>24</sup> The reasons why a prior MGUS diagnosis could lead to better survival in multiple myeloma patients remains unclear.

## **GUIDELINES FOR MONITORING AND MANAGEMENT**

There are no clear standard recommendations for MGUS clinical follow-up. For patients with a diagnosis of MGUS, optimal clinical follow-up, including the frequency of visits and the type of ancillary tests to order, is unknown.<sup>25</sup> There are four international clinical practice guidelines for MGUS, all based on expert consensus, yet their recommendations vary widely.<sup>26-29</sup> The United Kingdom Myeloma Forum and Nordic Myeloma Study Group (UK-Nordic)<sup>26</sup> and the international expert consensus (IEC)<sup>27</sup> recommend more aggressive follow-up patterns than the International Myeloma Working Group (IMWG)<sup>30</sup> and the European Myeloma Network (EMN),<sup>28</sup> which offer more conservative guidelines. In general, these guidelines suggest, depending on the individual patient's characteristics, life-long monitoring every 6 to 12 months of individuals to detect progression to multiple myeloma or related disorders.<sup>26-29</sup> For example, low-risk (i.e., a < 30 g/L of M protein on serum protein electrophoresis test) MGUS requires less frequent monitoring than patients in higher risk strata.<sup>24</sup> The most commonly used diagnostic tests for MGUS are serum or urine protein electrophoresis (SPE), immunofixation, and in more recent years, serum free light chain testing (SFLC).<sup>31</sup>

## **FOLLOW-UP PATTERNS IN THE UNITED STATES**

In the US, MGUS follow-up patterns vary by geographic region, sex, gender, and age.<sup>32,33</sup> Patients  $\geq 80$  years old were more likely to be followed up at intervals of <6 months while patients  $\geq 60$  years were followed up at intervals of <13 months.<sup>32</sup> Also,

patients from the Northeastern US were more likely to be followed up at intervals >24 months, which is longer than any other US region.<sup>32</sup> Approximately half the patients with MGUS diagnosed in 2013 lacked concordance with any of the clinical practice guidelines.<sup>33</sup> The role of other clinical characteristics, such as diagnosed comorbidities, in clinical follow-up patterns is not well established, mainly because MGUS is incidentally diagnosed, and people with other chronic conditions may be more likely to be diagnosed with MGUS as a result of frequent encounters with the healthcare system.<sup>34</sup> In the **first aim** of this dissertation, we characterized trajectories of change in creatinine and hemoglobin laboratory values to identify subgroups of patients with MGUS with certain patterns of common clinical biomarkers over time.

## **THE IMPACT OF A DIAGNOSIS OF MGUS ON HEALTHCARE UTILIZATION**

Patients may experience high distress after a diagnosis of premalignant MGUS.<sup>35-</sup><sup>37</sup> This associated anxiety could result in a change (overutilization/underutilization) in healthcare utilization and clinical surveillance beyond what is necessary.<sup>38</sup> Quantifying the care and surveillance of patients with MGUS is of clinical relevance given that multiple myeloma patients with a pre-existing MGUS diagnosis have been shown to have a better multiple myeloma prognosis. Healthcare utilization patterns by MGUS patients may provide insight into preventative healthcare measures that may improve their overall health and result in prolonged survival.<sup>39</sup> Therefore, in the **second aim** of this dissertation we investigated the role of an MGUS diagnosis in healthcare utilization patterns in order

to obtain insight into why patients with MGUS might have better long-term survival. Studies have shown that cancer patients have better outcomes if they had more utilization of primary care preceding the cancer diagnosis.<sup>40-43</sup> To our knowledge, no studies have evaluated the impact of an MGUS diagnosis on overall health service utilization, including emergency department, hospital and outpatient visits. Patients with MGUS have frequent outpatients visits<sup>25</sup> possibly due in part to higher stress after this diagnosis, and concern about progressing to multiple myeloma. This dissertation investigated specific health services used during these follow-up visits, with the goal of elucidating factors and practices that may contribute to a patient's overall prognosis.<sup>33</sup>

### **PATIENT AND PROVIDER PERCEPTIONS**

Finally, patient and provider perceptions of MGUS may be divergent. Based on prior work providers may describe MGUS to their patients with simple terminology such as “abnormal protein” and use analogies such as comparing the protein found in the blood (paraprotein) to the finding of a mole or lump.<sup>44</sup> In addition, providers have previously been found to include the terms premalignant, precancer or cancer less frequently when explaining MGUS to their patients. Patients' education level, age and cognitive ability have been shown to be important factors to providers in deciding how and whether information was relayed to patients.<sup>44</sup> In addition, it is important to understand patients' experiences after a diagnosis of MGUS. There is, however, a lack of data evaluating patient and healthcare provider responses to a new diagnosis of MGUS, which may

impact patients' healthcare utilization after the MGUS diagnosis. In our **third aim**, we seek to provide insight into the reasons for patients' healthcare utilization practices overall and related to MGUS and allow for the exploration of patient- and provider-level drivers behind patterns of healthcare utilization in addressing MGUS.

This dissertation had the overall goal of evaluating factors contributing to healthcare utilization in a population diagnosed with a premalignant condition and elucidate potential targets to improve long-term survival of MGUS patients. The specific aims were:

### **AIM 1**

Describe laboratory value trajectories of patients with MGUS diagnosed in a community-based practice in central Massachusetts.

***Hypothesis 1:*** Distinct longitudinal trajectories of values from commonly used laboratory tests (e.g. serum creatinine) will emerge in MGUS patients.

### **AIM 2**

Determine if an MGUS diagnosis is associated with changes in healthcare utilization (e.g., emergency department hospital, and outpatient visits) that differ according to



patients' sociodemographic and clinical characteristics as compared to a population without MGUS.

***Hypothesis 2:*** Compared to a comparison group matched on age, sex, and length of enrollment in the health system, as well as the time period before diagnosis, patients with MGUS will have increased healthcare utilization after MGUS diagnosis.

### **AIM 3**

Explore the patient- and provider-level drivers of healthcare utilization in patients with MGUS and factors associated with care-seeking practices.

**CHAPTER II:**

**MULTI-TRAJECTORY MODELS OF SERUM BIOMARKERS AMONG  
PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED  
SIGNIFICANCE**

**CHAPTER II: MULTI-TRAJECTORY MODELS OF SERUM BIOMARKERS  
AMONG PATIENTS WITH MONOCLONAL GAMMOPATHY OF  
UNDETERMINED SIGNIFICANCE**

**ABSTRACT**

**Background**

Understanding the progression of monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM) is needed to identify patients who would benefit from closer clinical surveillance. Given that two of the defining criteria of multiple myeloma are renal failure and anemia, we described the trajectories of creatinine (Cr) and hemoglobin (Hgb) over time in patients with a diagnosis of MGUS.

**Methods**

Patients diagnosed with MGUS (n=424) were identified by a previously validated case-finding algorithm using health claims and electronic health record data (2007-2015) and followed through 2018. Group-based trajectory modeling identified patients with distinct laboratory value trajectories of Cr (mg/dL) and Hgb (mg/dL).

**Results**

Most were non-Hispanic White (97.6%) with a mean age of 75 years at MGUS diagnosis. Three multi-trajectory groups were identified: 1) Normal Cr/Hgb (53.1%) -

stable serum Cr levels and decreasing, normal Hgb levels; 2) Normal Cr/lower-normal Hgb group (44.3%) - stable, slightly elevated levels of Cr and decreasing, slightly low levels of Hgb; and 3) High Cr/borderline Hgb group (2.6%) - increased Cr levels and stable low levels of Hgb. Patients with MGUS in the normal Cr/lower-normal Hgb group were older, more likely to have a prior cancer diagnosis, and had more comorbidities than participants in the normal Cr/Hgb group. Twenty-one patients developed multiple myeloma during the study period (normal Cr/Hgb: 3%, normal Cr/lower-normal Hgb: 7%, high Cr and borderline Hgb: 9%).

### **Conclusion**

Biomarker trajectories characterize specific subpopulations of patients with MGUS over time. Future research should further investigate how these trajectories may be related to the risk of progression to multiple myeloma, including M-protein levels.

## INTRODUCTION

Multiple myeloma (MM) is the second most commonly diagnosed hematologic malignancy in the United States.<sup>1-3</sup> Monoclonal gammopathy of undetermined significance (MGUS) is an early pathogenic step in the development of multiple myeloma, and a risk factor for other malignancies, including lymphoma, light chain amyloidosis, and Waldenström macroglobulinemia.<sup>17,45,46</sup> While 3% of adults over the age of 50 years may have clinical evidence of MGUS,<sup>30,47-51</sup> the vast majority remain undiagnosed, as MGUS is mostly asymptomatic and almost always diagnosed incidentally.<sup>24,45,52</sup> Patients with MGUS progress to multiple myeloma at a rate of approximately 1% annually.<sup>22,53,38</sup> Despite the relatively low risk of progression, patients with a diagnosis of MGUS are generally followed up every 6-12 months for signs of progression to malignancy.<sup>35-37</sup>

It is not currently possible to predict which patients with MGUS are more likely to progress to multiple myeloma.<sup>54</sup> Elevated monoclonal (M)-protein concentration,<sup>38</sup> immunoglobulin M or A isotype,<sup>38</sup> abnormal bone marrow plasma cells<sup>55,56</sup> and abnormal free light chain ratios are risk factors for progression of MGUS to multiple myeloma.<sup>57</sup> Gaining a better understanding of factors related to the progression of MGUS to multiple myeloma is essential to identify patients at greater risk of progression and provide insights into which patients with MGUS will benefit from closer surveillance.

The absence of end-organ, as damage defined by the CRAB criteria (hyperCalcemia, Renal insufficiency, Anemia, lytic Bone lesions) is a key clinical feature distinguishing MGUS from multiple myeloma.<sup>58</sup> Two of the critical defining criteria of multiple myeloma are renal failure (as measured by creatinine (Cr) > 2.0 mg/dl) and anemia (hemoglobin (Hgb) < 10 g/dL).<sup>45,59</sup> Discerning disease patterns through the use of rigorous statistical models has the potential to identify distinct subgroups of patients. Using data from patients seeking care at a large provider group in central Massachusetts, we used group-based trajectory modeling (GBTM) to identify groups of patients with MGUS who shared similar trajectories over time of two commonly measured biomarkers indicative of renal failure and anemia, Cr and Hgb. A secondary study goal was to examine differences in patient characteristics among patients diagnosed with MGUS with varying biomarker trajectories.

## METHODS

### Study Participants and Settings

The Institutional Review Board of the University of Massachusetts Medical School approved this study. It was conducted in the Meyers Primary Care Institute (MPCI), a joint research endeavor of the University of Massachusetts Medical School (UMMS), Fallon Health, an insurer, and Reliant Medical Group, a community-based multispecialty provider organization. A standardized data resource comprised of electronic health records (EHR) and health claims data for patients receiving care at Reliant Medical Group from January 1, 1999, through December 31, 2018, was used to identify the study population.<sup>60</sup> Cancer diagnoses through 2016 were identified using tumor registry data obtained from the Massachusetts Cancer Registry (1999-2016) and the in-house tumor registry at Reliant (2010-2016).

### Study Population

This analysis included individuals diagnosed with MGUS who were identified by applying a case-finding algorithm to the EHR-based database, as previously described elsewhere.<sup>61</sup> Briefly, the algorithm first identified all eligible patients aged 50 years and older with  $\geq 2$  ICD-9 diagnosis codes for MGUS (273.1) entered on different dates within 12 months between 2007 and 2015. Next, patients were selected who, within 90 days of MGUS diagnosis, had at least one code for a serum or urine protein electrophoresis test (Current Procedural Terminology (CPT) code 84155 or 84156), at least one serum or

urine immunofixation test (CPT 86334 or 86335), and an in-office hematology/oncology visit. Patients met the algorithm criteria if the corresponding CPT code was present in their EHR within the specified time frame. The algorithm identified 429 cases of MGUS and 424 had at least two measures of Cr and Hgb (Supplemental Figure 1).

### **Covariates**

The first appearance of the ICD-9 diagnosis code for MGUS (273.1) in a patient's EHR was considered the diagnosis date. The following characteristics were assessed at diagnosis date: age, sex (male and female), and race (non-Hispanic White, non-Hispanic Black and other race/ethnicities), Charlson comorbidity index (continuous [0-15 score]; and categorical [0,1, 2+] scores),<sup>62</sup> smoking status (never, current, or quit/former/passive smokers), body mass index (BMI) (underweight [ $<18.5$  kg/m<sup>2</sup>], normal [18.5-25 kg/m<sup>2</sup>], overweight [25-30 kg/m<sup>2</sup>], obese [ $\geq 30$  kg/m<sup>2</sup>]), alcohol use (never and current), and census tract-level socioeconomic index (low, medium, high). The Charlson comorbidity index score was calculated based on ICD-9/10 codes in the year before the MGUS diagnosis date. Those patients without any of the ICD codes included in the Charlson comorbidity index were assigned the value of zero (Supplemental Table 1). The census tract-level socioeconomic index was calculated using factor analysis of median household income, median house rent, percentage of the population living below 150% of the poverty line, education index, and percent unemployed. We calculated the tertiles of socioeconomic index values (i.e., first tertile = low neighborhood SES, the second tertile = medium neighborhood SES, third = high neighborhood SES).<sup>63</sup> All data were derived



from the EHR and claims data of MGUS cases. To account for missing data related to tobacco use, alcohol use, and BMI, we imputed values by carrying forward the last available observation closest to the MGUS diagnosis date.<sup>64</sup>

### **Laboratory values**

We evaluated the trajectories of the laboratory results of serum Cr and Hgb tests. We collected all available measures of these laboratory test values through the review of the patients' EHR collected over three years after MGUS diagnosis for each patient. The primary analysis focused on measurements collected on or after the patient's date of MGUS diagnosis. All outcome variables (Cr and Hgb) were averaged every six months from diagnosis date to deal with the relative scarcity of data and infrequency of the laboratory measurements. This procedure also yields measurements on a discrete time scale required by the GBTM.

### **Statistical Analysis**

Descriptive statistics were used to evaluate the sociodemographic and clinical characteristics of patients with MGUS. We performed a multi-trajectory analysis using the TRAJ procedure in Stata 16.<sup>65</sup> A series of group-based trajectory models were separately fitted and compared to determine the optimal number of subgroups defined by serum Cr and Hgb levels, and models with 2-5 groups were analyzed. We started the full model with cubic polynomials and then reduced the order of each group until the parameters of the trajectories were statistically significant (p-value <0.05). For each

model, we obtained the fit statistics (Bayesian Information Criterion, Akaike Information Criterion, and Log-Likelihood), the proportion of patients assign to each trajectory group and the mean posterior probability for each group. After considering model fit, parsimony, and clinical relevance, we considered the best-fitting model for Cr and Hgb separately, given that for Cr the best model was a four-group model and for Hgb the best was a three-group model (Data not shown). Then, we fit models with three and four multi-trajectory groups evaluating both outcomes (Cr and Hgb) together. This approach fits a semiparametric (discrete) mixture model to longitudinal data using the maximum likelihood function where each resultant joint trajectory is a combination of the individual trajectories for Cr and Hgb. After comparing the model selection statistics and graphical representation, we considered that the most parsimonious model was the one with three group trajectories. The final orders of polynomials for Cr were one group with a cubic and two groups with intercept, and for Hgb the order for all three groups were cubic. Patients with MGUS were assigned to the trajectory groups for which they had the highest posterior probabilities as predicted by the model. We assigned qualitative labels to describe each group based on the overall patterns of Cr and Hgb trajectories. Multinomial logistic regression was used to identify the bivariate associations of group trajectories (outcome) with characteristics at time of diagnosis (predictors). Logistic regression model were used to evaluate the association of multiple myeloma (outcome) and trajectory groups (predictor). The models are also adjusted for comorbidity index and age. As a sensitivity analysis, we repeated all analyses with the subset of 154 identified MGUS cases validated by a targeted chart review.

## RESULTS

### Study population characteristics

The 424 patients with MGUS had a median (IQR) follow-up time of 22 (12-31) months, with 71% (Hgb) to 75% (Cr) of patients with lab test results had at least three years of follow-up. Of the identified MGUS cases, nearly half were female, most were non-Hispanic White, and the mean age at MGUS diagnosis was 75.0 years. Eleven percent were current smokers, 46.3% were current alcohol users, and 70% were overweight or obese. The majority of patients with MGUS did not have a previous diagnosis of cancer and had a median Charlson comorbidity index of 2.3 (Table 1).

### Predicted multi-trajectory groups of creatinine and hemoglobin laboratory values

The median number of repeat tests for Hgb was 6 (range: 2-6) and for Cr, 6 (range: 2-6) tests per participant. Three distinct multi-trajectory groups were identified (Figure 1). Patients in the *Normal Cr/Hgb* group (n= 225, 53.1%) showed stable normal levels of serum Cr over time (mean: 1.1 mg/dL) and a slight decrease in mean Hgb levels of approximately 0.1 mg/dL per year on average. The *Normal Cr/ Lower-normal Hgb* group (n= 188, 44.3%) showed stable normal levels of serum Cr over time (mean: 1.4 mg/dL) and slight decrease in mean Hgb levels of approximately 0.01 mg/dL per year on average. Patients in the *High Cr/ borderline Hgb* group (n= 11, 2.6%) had increases of

approximately 1.0 mg/dL per year on average in Cr and decreasing levels of Hgb over time.

### **Predictors of group membership of creatinine and hemoglobin trajectories**

Patients with MGUS in the normal Cr/Hgb group (N = 225; mean = 72 years) were younger than patients with MGUS in the normal Cr / lower-normal Hgb group (N = 188; mean = 79 years, p-value = 0.0001). However, the age at diagnosis of patients with MGUS in the normal Cr/Hgb group is not statistically different from patients with MGUS in the high Cr/ borderline Hgb group (N = 11; mean = 69 years; p-value=0.385). Patients with MGUS in the normal Cr/Hgb group had lower mean Charlson comorbidity score (mean Charlson score = 1) than patients in the normal Cr / lower-normal Hgb group (mean Charlson score = 3, p-value=0.001). Patients with MGUS in the normal Cr/Hgb group also had a lower mean Charlson score than patients in the high Cr/ borderline Hgb group (mean score = 6, p-value=0.0001; Table 2).

### **Progression to multiple myeloma by trajectory group**

In an exploratory analysis examining a limited number of multiple myeloma diagnoses among study participants (with an average of 10 years of follow-up), 21 patients developed multiple myeloma after MGUS diagnosis. Six multiple myeloma cases were in the normal Cr/Hgb group, fourteen were in the normal Cr/ lower-normal

Hgb group, and one was in the high Cr/ borderline Hgb group. We constructed a logistic regression model with multiple myeloma as the outcome and trajectory group as the main independent variable to explore a possible association, although precision was low. After adjusting for Charlson comorbidity index and age at diagnosis, patients in the high Cr / borderline Hgb group (aOR: 5.22, 95% CI = 1.78-15.32) and normal Cr / lower-normal Hgb group (aOR: 12.28; 95% CI = 1.03-146.05) were more likely to eventually be diagnosed with multiple myeloma than patients in the normal Cr/Hgb group (Table 3).

#### **Sensitivity analysis with validated MGUS**

Analyses on the subset of 154 patients whose MGUS diagnosis was validated via a chart review are shown in Supplemental Figure 1-2, Supplemental Tables 2-3.

Qualitatively, the findings were similar in the group of patients with validated MGUS as with the larger sample.

## DISCUSSION

In this study, we identified three distinct groups of patients with MGUS sharing similar trajectories of Cr and Hgb laboratory values over the three years following a diagnosis of the premalignant, yet asymptomatic condition MGUS. We found that few patients transitioned to multiple myeloma. Guidelines for monitoring patients with MGUS encourage clinicians to track certain blood markers every 6-12 months, including M-protein levels, that may indicate progression to malignancy. However, there are four existing international guidelines for the clinical surveillance of patients with MGUS, and specific recommendations vary.<sup>26-29</sup>

In the US, MGUS follow-up practice patterns vary by geographic region, sex, and age.<sup>32,33</sup> A recent study observed that patients aged  $\geq 80$  years old with an MGUS diagnosis were more likely to be followed clinically at intervals of  $< 6$  months, while patients  $\geq 60$  years were followed up at intervals of  $> 13$  months.<sup>32</sup> Patients from the northeastern US were more likely to be followed up at intervals  $> 24$  months, which is longer than any other US region.<sup>32</sup> Approximately half the patients with MGUS diagnosed in 2013 in the US lacked concordance with any of the clinical practice guidelines.<sup>33</sup> Our study was conducted in Massachusetts and as such may be limited by longer follow-up intervals typical in the northeast region of the US.<sup>33</sup>

The most common tests for diagnosing patients with MGUS are serum or urine protein electrophoresis, immunofixation, and in more recent years, serum free light chain testing.<sup>3,1</sup> In addition, Cr and complete blood cell count tests are recommended as part of regular clinical surveillance to monitor potential organ damage indicative of disease progression.<sup>26-29</sup> The ability to identify longitudinal patterns of these laboratory values could help define additional, informative criteria to follow-up in these patients.

To the best of our knowledge, this study is the first study to simultaneously model Cr and Hgb levels among patients with MGUS. We were unable to evaluate M protein levels in this population, as relevant results generally appear as text, and were not available in our EHR-based datasets. The three groups identified by our models are characterized by distinct trajectories and patient demographic characteristics. A previous study among patients with smoldering multiple myeloma found decreased trajectories for Hgb associated with a decreased median time to progression.<sup>66</sup> However, no studies have evaluated trajectories of Cr levels among patients with a multiple myeloma precursor condition, or modeled the two biomarkers together.

### **Study Strengths and Limitations**

This study has several strengths, including the use of a large, standardized electronic database of claims and EHR data. This database allowed us to obtain objective measurements and longitudinal follow-up. In addition, the utilization of a validated MGUS algorithm allowed for the identification of patients with MGUS in a community-

based setting with reasonable accuracy.<sup>61</sup> In addition, we used GBTM,<sup>65</sup> a tool that has been increasingly adopted in clinical research, to model the development of a clinically important indicator over time, with the goal of identifying groups of individuals sharing a common trajectory.<sup>67</sup> The limitations that should be considered in the interpretation of the results include the generalizability to other populations (the majority of this population were non-Hispanics White patients, and all had access to healthcare) and the limited sample size. We were unable to validate all MGUS cases identify by the algorithm, however a sensitivity analysis of validate MGUS cases by EHR review (n=154) yielded similar results. In addition, we did not independently verify the EHR-derived data present in the datasets, and we acknowledge the possibility of wrongly encoded lab values. We were also unable to assess other important relevant laboratory values including M-protein levels which were not captured in the database. Cancer diagnoses were only available through 2016. At this time, we cannot apply the trajectory models reported in this study to predict the risk of progression to multiple myeloma for a patient with MGUS. Future, larger studies are needed to specifically develop methodologies to accurately predict patients' risk of progression to multiple myeloma, including identifying early signs of multiple myeloma progression.

## **Conclusion**

This study shows that GBTM can be used to identify sub-groups of patients with MGUS with distinct trajectories of important disease biomarkers. Future research should further investigate how these trajectories may be related to the risk of progression to



multiple myeloma, including M-protein levels. Furthermore, our study revealed distinct clinical and sociodemographic factors related to trajectory group. If validated in larger diverse populations with more MGUS cases the trajectories could be refined and included additional biomarkers such as M-protein and help in the development of better surveillance guidelines for patients with MGUS.

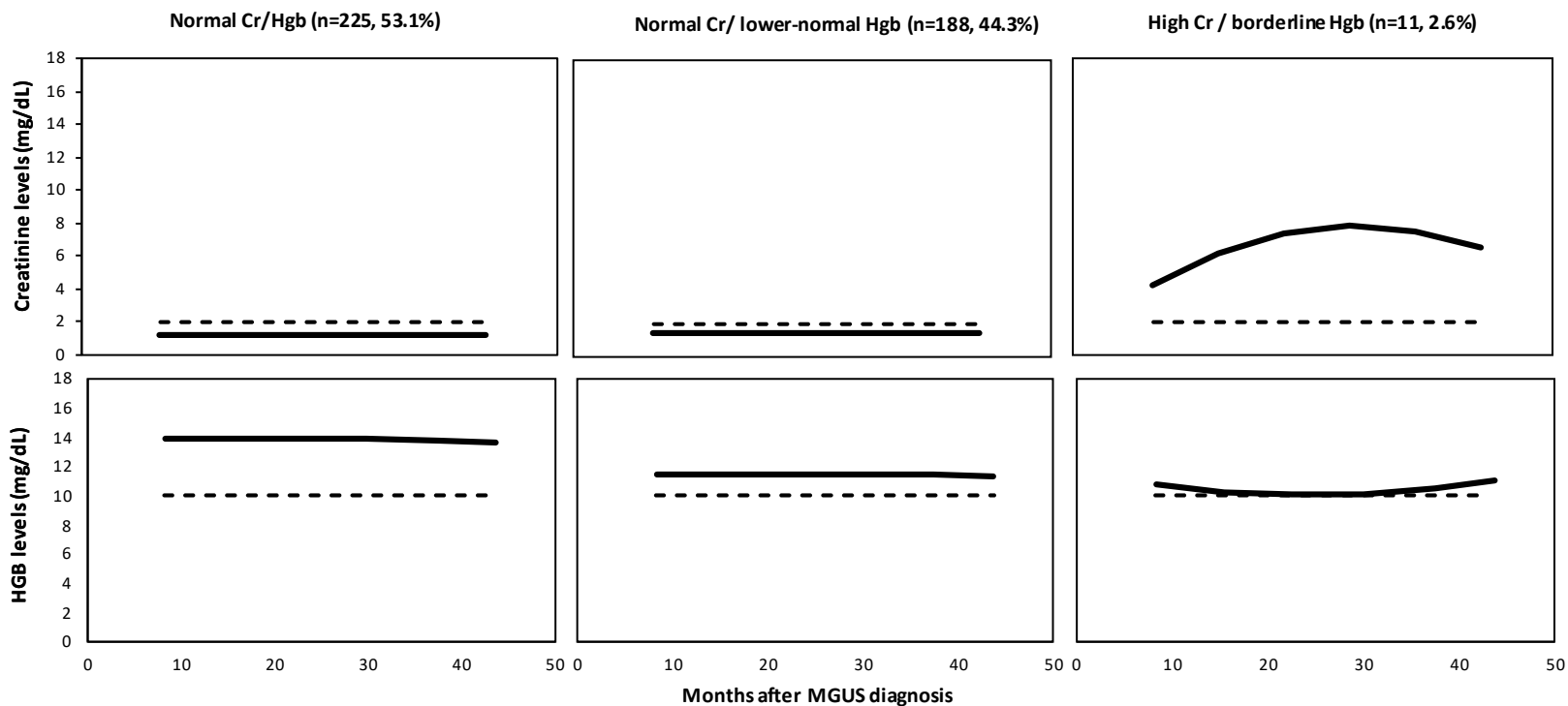
## TABLES AND FIGURES

**Table 1.** Sociodemographic and clinical characteristics at MGUS diagnosis of patients with MGUS

<b>Characteristic</b>	<b>Patients with MGUS (n=424)</b>
<b>Men, n (%)</b>	216 (50.9)
<b>Age at index date (Mean ± S.D.), years</b>	75.0 ± 10.4
<b>Race, n (%)</b>	
Non-Hispanic White	364 (97.6)
Non-Hispanic Black	6 (1.6)
Other	3 (0.8)
<b>Socioeconomic index, n (%) <sup>a</sup></b>	
Low	82 (37.8)
Medium	63 (28.6)
High	75 (34.1)
<b>Tobacco use, n (%)</b>	
Never	149 (38.2)
Current smokers	42 (10.8)
Quit/Former/Passive Smokers	199 (51.0)
<b>Current alcohol use, n (%) <sup>b</sup></b>	149 (46.3)
<b>Body mass index, n (%)</b>	
Underweight (<18.5 kg/m <sup>2</sup> )	6 (1.7)
Normal (18.5-25 kg/m <sup>2</sup> )	102 (28.4)
Overweight (25-30 kg/m <sup>2</sup> )	141 (39.3)
Obese (≥30 kg/m <sup>2</sup> )	110 (30.7)
<b>Previous cancer diagnosis, n (%) <sup>c</sup></b>	
Breast (among women)	11(5.2)
Prostate (among men)	13 (6.0)
Blood <sup>d</sup>	4 (0.9)
Other	15 (3.5)
<b>Charlson comorbidity index, n (%) <sup>e</sup></b>	
0	108 (25.5)
1	78 (18.4)
≥ 2	238 (56.1)
Mean ± SD	2.3 ± 2.3
<b>Mean serum Cr levels, (± S.D.), mg/dl <sup>f</sup></b>	1.3 ± 1.0
<b>Mean serum Hgb levels, (± S.D.), mg/dl <sup>g</sup></b>	12.5 ± 1.5

May not total 100% due to rounding. Cr=creatinine; Hgb= Hemoglobin. Missing values: Race (n=51), socioeconomic status index (n=204), tobacco (n=34), alcohol (n=102), body mass index (n=65) <sup>a</sup> Tertiles of factor score of median household income, median house rent, percentage of the population living below 150% of the poverty line, education index, and percent unemployed; <sup>b</sup> Current vs never <sup>c</sup> presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis; <sup>d</sup> Includes multiple myeloma, leukemia, lymphoma; <sup>e</sup> Using a modified Charlson score with 15 components; <sup>f</sup> Normal levels less than 2mg/d; <sup>g</sup> Normal levels between 12 and 15 mg/dl

**Figure 1.** Multi-trajectories of creatinine and hemoglobin among 424 patients with MGUS identified through EHR data



The dashed-line (----) represents the cut-off point for the definition of abnormal values for each biomarker. Renal insufficiency is defined as creatinine (Cr) levels  $>2$  mg/dl. Anemia is defined as hemoglobin (Hgb) levels  $<10$  mg/dL.

**Table 2.** Characteristics at MGUS diagnosis according to predicted trajectory group

Characteristic	Normal Cr/Hgb	Normal Cr/ Lower-Normal Hgb	High Cr/ borderline Hgb
<b>Total, n (%)</b>	225 (53.1)	188 (44.3)	11 (2.6)
<b>Men, n (%)</b>	121 (53.8)	88 (46.8)	7 (63.6)
<b>Age at index date (Mean ± S.D.), years</b>	72.1 ± 10.5	78.8 ± 8.7	69.3 ± 10.2
<b>Race, n (%)</b>			
Non-Hispanic White	203 (96.7)	155 (98.7)	6 (100)
Non-Hispanic Black	4 (1.9)	2 (1.3)	0
Other	3 (1.4)	0	0
<b>Socioeconomic index, n (%)<sup>a</sup></b>			
Low	44 (36.7)	36 (38.7)	2 (28.6)
Medium	31 (25.8)	30 (32.3)	2 (28.6)
High	45 (37.5)	27 (29.0)	3 (42.9)
<b>Tobacco use, n (%)</b>			
Never	79 (38.5)	67 (38.5)	3 (27.3)
Current smokers	30 (14.6)	10 (5.7)	2 (18.2)
Quit/Former/Passive Smokers	96 (46.8)	97 (55.7)	6 (54.5)
<b>Current alcohol use, n (%)<sup>b</sup></b>	95 (54.9)	53 (37.1)	1 (16.7)
<b>Body mass index, n (%)</b>			
Underweight (<18.5 kg/m <sup>2</sup> )	2 (1.0)	4 (2.5)	0
Normal (18.5-25 kg/m <sup>2</sup> )	56 (29.5)	45 (28.1)	1 (11.1)
Overweight (25-30 kg/m <sup>2</sup> )	79 (41.6)	58 (36.2)	4 (44.4)
Obese (≥30 kg/m <sup>2</sup> )	53 (27.9)	53 (33.1)	4 (44.4)
<b>Previous cancer diagnosis, n (%)<sup>c</sup></b>			
Breast (Among women)	3 (2.9)	7 (7.0)	1 (9.1)
Prostate (Among men)	3 (2.5)	9 (10.2)	1 (9.1)
Blood <sup>d</sup>	2 (0.9)	2 (1.1)	0
Other	5 (2.2)	9 (4.8)	1 (9.1)
<b>Charlson comorbidity index, n (%)<sup>e</sup></b>			
0	80 (35.6)	28 (14.9)	0
1	56 (24.9)	22 (11.7)	0
≥ 2	89 (39.6)	138 (73.4)	11 (100)
Mean ± SD	1.5 ± 1.8	3.1 ± 2.5	5.8 ± 2.6
<b>Serum Cr, (Mean ± S.D.), mg/dl<sup>f</sup></b>	1.0 ± 0.4	1.3 ± 0.5	6.5 ± 2.2
<b>Serum Hgb, (Mean ± S.D.), mg/dl<sup>g</sup></b>	13.7 ± 0.9	11.3 ± 0.9	10.5 ± 0.7

May not total 100% due to rounding. Cr=creatinine; Hgb= Hemoglobin. Missing values: Race (n=51), socioeconomic status index (n=204), tobacco (n=34), alcohol (n=102), body mass index (n=65) <sup>a</sup> Tertiles of factor score of median household income, median house rent, percentage of the population living below 150% of the poverty line, education index, and percent unemployed; <sup>b</sup> Current vs never; <sup>c</sup> presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis; <sup>d</sup> Includes multiple myeloma, leukemia, lymphoma.; <sup>e</sup> Using a modified Charlson score with 15 components; <sup>f</sup> Normal levels less than 2mg/d; <sup>g</sup> Normal levels between 12 and 15 mg/dl

**Table 3.** Logistic regression models of the association between trajectory group and multiple myeloma.

<b>Trajectory group</b>	<b>Multiple myeloma</b>	<b>Crude OR (95% CI)</b>	<b>Adjusted OR (95% CI) *</b>
Normal Cr/Hgb	6 (3%)	<b>Ref.</b>	<b>Ref.</b>
Normal Cr/normal-lower Hgb	14 (7%)	2.94 (1.10-7.80)	5.22 (1.78-15.32)
High Cr/borderline Hgb	1 (9%)	3.65 (0.40-33.27)	12.28 (1.03-146.05)

\*Adjusted for Charlson comorbidity index and age at diagnosis

**CHAPTER III:**

**DIFFERENCES IN HOSPITAL, EMERGENCY ROOM AND OUTPATIENT  
VISITS AMONG ADULTS WITH AND WITHOUT MONOCLONAL  
GAMMOPATHY OF UNDETERMINED SIGNIFICANCE**

# **CHAPTER III: DIFFERENCES IN HOSPITAL, EMERGENCY ROOM AND OUTPATIENT VISITS AMONG ADULTS WITH AND WITHOUT MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE**

## **ABSTRACT**

### **Background**

One percent of patients with monoclonal gammopathy of undetermined significance (MGUS) progress to multiple myeloma per year. To evaluate the impact of receiving an MGUS diagnosis on healthcare utilization, we compared hospital, emergency room (ER), and outpatient visits between patients with and without MGUS.

### **Methods**

A cohort of patients with MGUS identified by a recent algorithm (n=429) were matched on sex, age ( $\pm 2$  years) and length of enrollment in the health system (-12/+6 months), to a cohort of patients without MGUS (n=1,286). Three-time frames were assessed: one year before, one month before and after, and one year after diagnosis/index date. Multivariable conditional Poisson models were used to evaluate the magnitude of change of each service in patients with MGUS as compared to patients without MGUS.

## **Results**

Half the population was female, with a mean age at diagnosis/index date of 75 years. The majority was non-Hispanic White (MGUS:98%, non-MGUS:96%), and the mean Charlson comorbidity index score was higher for patients with MGUS than those without (2.3 versus 1.6, p-value<0.05). During the two-month period around diagnosis/index date, the rates of ER visits (Adjusted Incidence Rate Ratio [aIRR]:1.7, 95% CI:1.1-2.8), hospital visits (aIRR:4.7, 95% CI:2.8-7.8) and outpatient visits (aIRR:2.9, 95% CI:2.6-3.2) were higher for patients with MGUS than patients without MGUS. In the year following MGUS diagnosis, the association was attenuated, although still elevated.

## **Conclusions**

Our study suggests that MGUS diagnosis is associated with higher utilization of ER, hospital and outpatient visits, especially during the months surrounding the diagnosis date.



## INTRODUCTION

Multiple Myeloma (MM) is the second most common hematologic malignancy in the US and five-year survival is 54% in these patients.<sup>1-3</sup> Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant plasma cell disorder preceding the development of multiple myeloma.<sup>17,45,46</sup> This premalignant condition is asymptomatic, however, and is typically diagnosed incidentally through blood tests.<sup>24,45,52</sup> Patients with MGUS progress to multiple myeloma at a rate of approximately 1% annually,<sup>22,38,53</sup> yet despite the relatively low risk of progression, patients with MGUS are regularly followed up for signs of progression every 6-12 months.<sup>35-37</sup>

There are no screening programs available for MGUS detection, primarily due to a lack of treatment for MGUS and the relatively low probability of subsequent development of multiple myeloma.<sup>22,53,38</sup> Understandably, patients may experience high levels of stress after a diagnosis of MGUS,<sup>35-37</sup> which could result in changes in healthcare services utilization.<sup>68</sup> Furthermore, associated anxiety could result from the emotional burden which could cause someone to disengage completely with the healthcare system, or inversely, try to get more frequent follow-up care to monitor the potential progression to multiple myeloma.<sup>38</sup> There are multiple published MGUS follow-up guidelines with different recommendations, and thus follow-up care guideline for patients with MGUS may be variable.<sup>32</sup>

Quantifying the care and surveillance of patients with MGUS is of clinical relevance given that multiple myeloma patients with a pre-existing MGUS diagnosis have been shown to have a better multiple myeloma prognosis.<sup>24,52,69</sup> In addition, previous studies have shown that cancer patients have better outcomes if they had greater utilization of primary care preceding their cancer diagnosis.<sup>40-43</sup> Consequently, the elucidation of healthcare utilization patterns among MGUS patients may provide insight into how patients with MGUS differ clinically from patients without this diagnosis, and provide the first step in determining the factors that may contribute to their observed prolonged survival following a multiple myeloma diagnosis.<sup>39</sup>

There are limited studies evaluating the impact of a MGUS diagnosis on ER, hospital and outpatient visits. A previous study found that the number of self-reported ER visits was significantly lower in participants with MGUS compared to those without, while the number of self-reported hospital and outpatient visits were not significantly different between both groups.<sup>70</sup> The purpose of our this matched cohort study, using real-world data from patients seeking care at a large provider group practice in central Massachusetts, was to compare hospital, ER, and outpatient visits between a cohort of patients with MGUS and a cohort of patients without MGUS. We assessed the association across three time-frames: one year before diagnosis/index date, one month before and after diagnosis/index date, and one year after diagnosis/index date.

## **METHODS**

### **Study data**

This study was approved by the Institutional Review Board of the University of Massachusetts Medical School (UMMS). Informed consent was not required by study participants since this is a secondary analysis of a limited dataset derived from electronic health data. The data for this study were derived from the Virtual Data Warehouse (VDW) housed at the Meyers Primary Care Institute (MPCI), a research institute affiliated with the UMMS, Fallon Health, an insurer, and Reliant Medical Group (RMG), a community-based multispecialty provider organization. Additional data on cancer diagnoses were obtained from the Massachusetts Cancer Registry (1999-2016) and from an in-house tumor registry at RMG (2012-2018). The VDW is a standardized data resource which consists of electronic datasets populated with linked demographic, administrative, and outpatient laboratory test results, and healthcare utilization data (ambulatory visits and network and non-network hospital visits, including diagnoses and procedures) for patients receiving care at RMG from January 1, 1999 through December 31, 2018.<sup>60</sup>

### **Patients with MGUS**

This study includes 429 patients with MGUS who were identified through the application of a case-finding algorithm to the electronic health record (EHR)-based VDW database, previously detailed elsewhere.<sup>61</sup> Briefly, all patients with MGUS had at least

two MGUS diagnosis codes within 12 months in their EHR between January 2007 and December 2015, plus at least one serum or urine protein electrophoresis test, one immunofixation test, and at least one in-office visit with an oncologist within 90 days of MGUS diagnosis. Patients with a diagnosis of multiple myeloma at baseline (International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) morphology code 9732) or within 3 months following MGUS diagnosis were excluded.

### **Study design**

We used a matched cohort study design. For each patient with MGUS, three patients without MGUS were selected from a population-based sample of the active patient population included in the VDW.<sup>60</sup> Controls were matched to cases by age ( $\pm 2$  years), sex, and length of enrollment in the health system (12 months before and 6 months after index date). Patients without MGUS were enrolled in the study based on MGUS cases' first date of diagnosis, which became the patients without MGUS' index date. After matching was completed, one patient without MGUS was excluded because there was no evidence of healthcare utilization during the study period.

### **Outcomes**

The study outcomes were the total number of ER, hospital, and outpatient visits in the year before (30-365 days before), the months immediately adjacent to (30 days before and after), and one year after (30-365 days after) MGUS diagnosis/index date. The one year period after a diagnosis of MGUS was selected since most guidelines recommend

that people return for a follow-up visit within 6-12 months after diagnosis.<sup>26-29</sup> All ER, hospital and outpatient visits were extracted from EHR and claims data using Current Procedural Terminology (CPT) codes (Supplemental Table 1).

### **Statistical Analysis**

Descriptive statistics were used to compare sociodemographic and clinical characteristics of patients according to MGUS status. Continuous variables were compared using t-tests, while chi-square tests were used to compare categorical variables. Chi-square tests were also used to describe and compare characteristics of patients with or without MGUS diagnosis that had at least one ER, hospital, or outpatient visit. Descriptive statistics were used to describe the total use of services among patients with and without MGUS. In addition, the mean number of ER, hospital, and outpatient visits incurred by patients with MGUS were compared to patients without MGUS using a t-test.

We also evaluated other covariates that are known to be associated with a MGUS diagnosis or healthcare utilization, including sex (male/female), age at diagnosis/index date (continuous), race/ethnicity (non-Hispanic White vs. other race/ethnicities), tobacco use (never, quit/former/passive and current smoker), current alcohol use (yes/no), overweight/obese ( $>25$  kg/m<sup>2</sup>; yes/no), history of cancer diagnosis at baseline (breast, prostate, blood, other) identified by ICD-0-3 codes in EHR prior to MGUS diagnosis/index date, Charlson comorbidity index (categories: 0, 1,  $\geq 2$ ; and continuous). We used conditional Poisson regression, a method that has been previously used to analyze data

from matched cohort studies. This conditional fixed-effect modeling allows us to adjust for overdispersion and correlation between matched subjects.<sup>71,72</sup> Crude models and models adjusted for charlson comorbidity index categories were used to evaluate the total count of each category of healthcare utilization services (ER, hospital, and outpatient visits) among patients with MGUS as compared with their matched cohort of patients without MGUS.<sup>71,72</sup>

## RESULTS

### **Sociodemographic and clinical characteristics**

Because of matching, patients with MGUS and without MGUS were similar in almost all sociodemographic and clinical characteristics. More than half the patients were men (50.6%), with a mean age at diagnosis/index date of 75 years old. The majority were non-Hispanic White (96.9%). However, patients with MGUS had a significantly higher Charlson comorbidity index (2.3) than patients without MGUS diagnosis (1.6; p-value=0.0001) (Table 3).

### **Emergency department visits**

A significantly higher percent of patients with MGUS had at least one emergency department visit one year before (21.0% vs 10.3%; p-value<0.05), 30 days before and after (6.3% vs 2.9%; p-value<0.05) and one year after (23.3% vs 14.4%; p-value<0.05) MGUS diagnosis date than patients without MGUS (Table 1). Among those patients who had at least one emergency department visit, there was no significant difference in the average count of emergency department visit by MGUS status across all time periods (Table 4).

After adjusting for Charlson comorbidity index and race, patients with MGUS were 55% (IRR:1.55; 95% CI: 1.24 to 1.94) more likely to have an emergency department visit than patients without MGUS diagnosis one year before diagnosis/index date. During the 30 days before/after index day patients with MGUS were 74% (IRR: 1.74; 95% CI: 1.07 to 2.82) more likely to have an emergency department visit than patients without MGUS. Similar, yet slightly attenuated results were observed during the year after MGUS diagnosis/index date as patients with MGUS were 50% (IRR: 1.50; 95% CI: 1.24 to 1.820) more likely to have an emergency department visit than patients without MGUS (Table 5).

### **Hospital visits**

A significantly higher percent of patients with MGUS had at least one hospital visits one year before (14.0% vs 5.0%; p-value<0.05), 30 days before and after (4.7% vs 1.2%; p-value<0.05) and one year after (13.5% vs 8.8%; p-value<0.05) MGUS diagnosis date than patients without MGUS. Among patients who had at least one hospital visits during the year after MGUS diagnosis/index date, the average number of hospital visits was slightly higher for those with MGUS than patients without MGUS (4.1 vs 3.1; p-value = 0.001). However, no difference in the average number of hospital visits was observed by MGUS status before MGUS diagnosis/index date, and during the two-month period around diagnosis/index date (Table 4).



After adjusting for Charlson comorbidity index and race, patients with MGUS were two times (95% CI: 1.81 to 2.83) more likely to have a hospital visit than patients without MGUS one year before diagnosis/index date. During the 30 days before/after index date, patients with MGUS were five times (95% CI: 2.78 to 7.87) more likely to have a hospital visit than patients without MGUS, while during the year after MGUS diagnosis/index date patients with MGUS were 67% (95% CI: 1.40 to 1.99) more likely to have a hospital visit than patients without MGUS (Table 5).

#### **Office or outpatient visits**

There were no significant differences in the proportion of patients who had at least one outpatient visit during the year before (52.7% vs 51.1%) and the year after (62.2% vs 59.2%) MGUS diagnosis/index date. However, more patients with MGUS had at least one outpatient visit 30 days before/after diagnosis/index date (54.1% vs 32.6%) than patients without MGUS. Among patients who had at least one outpatient visit during all periods evaluated, the average number of outpatient visits was slightly higher for those with MGUS than patients without MGUS (Table 4).

After adjusting for Charlson comorbidity index and race, patients with MGUS were 27% (95% CI: 1.21 to 1.35) more likely to have an outpatient visit than patients without MGUS diagnosis one year before diagnosis/index date. During the 30 days before/after index date, patients with MGUS were three times (95% CI: 2.59 to 3.17)

more likely to have an outpatient visit than patients without MGUS, while during the year after MGUS diagnosis/index date patients with MGUS were 49% (95% CI: 1.42 to 1.57) more likely to have an outpatient visit than patients without MGUS (Table 5).

## DISCUSSION

In this matched cohort study of patients seeking care at a large provider group practice in central Massachusetts, we examined whether a diagnosis of MGUS was associated with differences in ER, hospital, and outpatient visits. We compared two matched patient groups: one with at least two MGUS diagnosis codes in their EHR data, and the other without any evidence of an MGUS diagnosis. We found that patients with MGUS had higher rates of ER, hospital and outpatient visits one year before and after and during the two-month period around MGUS diagnosis/index date. However, different patterns of utilization were observed within the different intervals. Patients with MGUS had higher rates of hospital visits than patients without MGUS one year before, and during the one-month period around MGUS diagnosis/index date. However, a higher proportion of ER and outpatient visits were only higher among patients with MGUS during the two-month period around MGUS diagnosis/index date.

After adjusting for comorbidities, patients with MGUS had higher rates of ER utilization, and more hospital and outpatient visits than patients without MGUS. In contrast, a similar study among adults 70 years or older found that patients with MGUS were 24% less likely to have an ER visit than patients without MGUS after approximately four years after diagnosis, and did not find differences between groups in hospital and outpatient visits.<sup>70</sup> The conflicting results could be due to several reasons. First, our study used an EHR-based case-finding algorithm to identify cases with MGUS

using EHR and claims data, with diagnosis date defined as the first time a MGUS diagnostic code was identified in the EHR. In contrast, the previous study used data from a random sampling of community residents at North Carolina, with participants identified with MGUS diagnoses identified through retrospective analysis of blood samples, without a requirement for a clinical diagnosis.<sup>70</sup> Second, we assessed healthcare utilization in three time-frames: one year before diagnosis/index date; one month before and one month after diagnosis/index date; and one year after diagnosis/index date. In contrast, patients for the previous study were asked to recall their past year healthcare utilization practices, four years after MGUS detection.<sup>70</sup> We found that the healthcare utilization was higher in the one-month period around MGUS diagnosis/index date, while a decrease of healthcare utilization was evident in the year after MGUS diagnosis. These reasons could explain why our results differ from previous reported results.<sup>70</sup>

The higher rate of ER and hospital visits among patients with MGUS in comparison with patients without MGUS could be explained is most likely due to symptoms unrelated to MGUS, because MGUS is largely asymptomatic. However in rare cases, patients could experience tingling, weakness or numbness related to the diseases process.<sup>73</sup> In addition, patients with undiagnosed MGUS may experience unrelated symptoms of pain, anemia, or kidney problems,<sup>34</sup> which could motivate those patients to seek urgent care, leading them to be diagnosed with MGUS. These observations could also explain why we observed an increase in utilization closer to MGUS diagnosis date, followed by a decrease during the year after diagnosis. Furthermore, the observed

increase in outpatient visits after diagnosis among patients with MGUS found in multivariable models may indicate MGUS follow-up appointments; however, we were not able to identify the reasons for outpatient visits in the available data.

### **Study Strengths and Limitations**

This study has several notable strengths including the use of a matched cohort study design of MGUS with extensive longitudinal real-world clinical data to evaluate healthcare utilization before and after MGUS diagnosis. The analyses used objective data derived from EHRs and not self-report, which could introduce recall bias. These data allowed us to obtain objective measurements and longitudinal follow-up. We also acknowledge several limitations to this study. Since MGUS is almost always diagnosed incidentally, cases of MGUS were limited to those patients who sought medical care and may not be representative of patients with undetected MGUS. While MGUS diagnosis was confirmed in a sample of our population by EHR review, we were unable to review the EHRs of all patients, and thus some of our cases may have been false positives. In addition, the study population was largely non-Hispanic White patients, and future studies should be conducted in more diverse populations. The use of electronic health data has several limitations including missing variables, as data are collected as part of medical care and not for research purposes. In addition, within our database, we were unable to determine whether outpatient visits were specifically for MGUS follow up, which would have allowed us to further investigate MGUS-specific healthcare utilization.

## **Conclusion**

This study provides additional knowledge on the role of an MGUS diagnosis in healthcare utilization in this population. This study shows that patients with MGUS are more engaged with the healthcare system than patients without MGUS, particularly around the time of MGUS diagnosis. This pattern of care could be a potential explanation for how patients arrive at an MGUS diagnosis, since the condition itself is largely asymptomatic. In addition, greater patient engagement could explain in part why patients with multiple myeloma with a previous MGUS diagnosis may have better prognosis.<sup>24,52,69</sup> However, future studies evaluating comorbid conditions related to MGUS diagnosis and follow-up are needed to understand reasons behind differences in health services patterns incurred by these patients. Additional research is needed to understand the mechanisms behind healthcare utilization and potential clinical and sociodemographic characteristics that may lead to improvement in the long-term overall health of patients with MGUS, including in larger and more diverse populations of patients with validated MGUS diagnoses.

## TABLES AND FIGURES

**Table 3.** Sociodemographic and clinical characteristics of patients according to monoclonal gammopathy of undetermined significance status.

<b>Characteristics at diagnosis/index date</b>	<b>Patients with MGUS (n=429)</b>	<b>Patients without MGUS (n=1,286)</b>	<b>p-value</b>
<b>Men, n (%)</b>	217 (50.6)	650 (50.5)	0.99
<b>Age at index date (Mean <math>\pm</math> SD), year</b>	74.9 $\pm$ 10.4	74.8 $\pm$ 10.4	0.84
<b>Race, n (%)</b>			
Non-Hispanic White	365 (97.6)	1,042 (96.2)	0.28
Non-Hispanic Black	6 (1.6)	19 (1.7)	
Other	3 (0.8)	22 (2.0)	
<b>Cancer diagnosis <sup>a</sup></b>			
Breast	8 (1.9)	34 (2.6)	0.11
Prostate	9 (2.1)	22 (1.7)	
Blood <sup>b</sup>	3 (0.7)	1 (0.1)	
Other	12 (2.8)	51 (4.0)	
<b>Charlson comorbidity index</b>			
0	110 (25.6)	504 (39.2)	0.0001
1	80 (18.6)	261 (20.3)	
2+	239 (40.5)	521 (40.5)	
<i>Mean <math>\pm</math> SD</i>	2.3 $\pm$ 2.3	1.6 $\pm$ 1.9	0.0001

May not total 100% due to rounding. Missing values for race (patients with (n=55) and without (n=203) MGUS). <sup>a</sup> Presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis/index date; <sup>b</sup> Leukemia, non-Hodgkin lymphoma.

**Table 4.** Total number of participants with at least one visit (n) and average count of services per person among patients with MGUS and matched patients without MGUS.

Healthcare service	Patients with MGUS			Patients without MGUS <sup>a</sup>			P-value <sup>d</sup>
	n (%) <sup>b</sup>	Mean ± SD <sup>c</sup>	Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	n (%) <sup>b</sup>	Mean ± SD <sup>c</sup>	Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	
<b>One year before diagnosis/index date<sup>^</sup></b>							
Emergency department visits*	90 (21.0)	1.67 ± 0.97	1 (1-2)	133 (10.3)	1.68 ± 1.41	1 (1-2)	0.92
Hospital visits*	60 (14.0)	3.78 ± 3.11	3 (2-5)	64 (5.0)	3.33 ± 2.88	2 (2-3.5)	0.40
Office or outpatient visits	226 (52.7)	9.02 ± 6.60	8 (4-12)	657 (51.1)	6.19 ± 4.57	5 (3-8)	<0.05
<b>30 days before and after diagnosis/index date<sup>^</sup></b>							
Emergency department visits*	27 (6.3)	1.33 ± 1.06	1 (1-1)	38 (2.9)	1.29 ± 1.10	1 (1-1)	0.78
Hospital visits*	20 (4.7)	2.70 ± 1.89	2 (1.5-3.5)	15 (1.2)	2.47 ± 1.12	2 (2-3)	0.67
Office or outpatient visits*	232 (54.1)	3.65 ± 2.10	3 (2-5)	419 (32.6)	1.89 ± 1.23	2 (1-2)	<0.05
<b>One year after diagnosis/index date<sup>^</sup></b>							
Emergency department visits*	100 (23.3)	1.85 ± 1.76	1 (1-2)	185 (14.4)	1.78 ± 1.85	1 (1-2)	0.76
Hospital visits*	58 (13.5)	4.14 ± 3.39	3 (2-6)	113 (8.8)	3.11 ± 2.30	2 (2-4)	<0.05
Office or outpatient visit	267 (62.2)	9.87 ± 6.79	8 (5-13)	761 (59.2)	6.31 ± 5.07	5 (3-8)	<0.05

<sup>a</sup> Participants were matched on age, sex and length of enrollment in the health system <sup>b</sup>n= total of patients with at least one healthcare service (emergency, hospital, or office/outpatient visits). <sup>c</sup> The mean, standard deviation (SD), median, and 25<sup>th</sup> – 75<sup>th</sup> percentile reported is among those with at least one of those services <sup>d</sup> t-test comparing means of total number of healthcare services of cases vs controls. \* $\chi^2$  test p-value < 0.05 <sup>^</sup>Time periods are not overlapping: One year before (30-365 days before), the months immediately adjacent to (30 days before and after), and one year after (30-365 days after) MGUS diagnosis/index date



**Table 5.** Magnitude of change in healthcare utilization among patients with MGUS as compared with their matched cohort of patients without MGUS, before, during and after MGUS diagnosis/index date using conditional Poisson regression.

Healthcare service	One year before diagnosis/index date <sup>^</sup>		30 days before and after diagnosis/index date <sup>^</sup>		One year after diagnosis/index date <sup>^</sup>	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
<b>Emergency department visits</b>	2.01 (1.63-2.47)	1.55 (1.24-1.94)	2.20 (1.43-3.39)	1.74 (1.07-2.82)	1.68 (1.40-2.01)	1.50 (1.24-1.80)
<b>Hospital visits</b>	3.20 (2.65-3.85)	2.23 (1.78-2.79)	4.38 (2.88-6.65)	4.76 (2.80-8.09)	2.04 (1.73-2.41)	1.65 (1.38-1.97)
<b>Office or outpatient visits</b>	1.50 (1.42-1.58)	1.27 (1.20-1.34)	3.21 (2.91-3.53)	2.86 (2.59-3.17)	1.65 (1.57-1.73)	1.48 (1.41-1.55)

\*Adjusted for Charlson comorbidity index and race, participants were matched on age, sex and length of enrollment in the health system (12 months before and 6 months after index date).<sup>^</sup> Time periods are not overlapping: One year before (30-365 days before), the months immediately adjacent to (30 days before and after), and one year after (30-365 days after) MGUS diagnosis/index date.

**CHAPTER IV:**

**PATIENT AND PROVIDER-LEVEL DRIVERS OF HEALTHCARE UTILIZATION  
RELATED TO A DIAGNOSIS OF MONOCLONAL GAMMOPATHY OF  
UNDETERMINED SIGNIFICANCE: A QUALITATIVE STUDY**

**CHAPTER IV: PATIENT AND PROVIDER-LEVEL DRIVERS OF HEALTHCARE  
UTILIZATION RELATED TO A DIAGNOSIS OF MONOCLONAL GAMMOPATHY  
OF UNDETERMINED SIGNIFICANCE: A QUALITATIVE STUDY**

**ABSTRACT**

**Background**

Monoclonal Gammopathy of undetermined significance (MGUS) is an asymptomatic, incidentally diagnosed precursor to multiple myeloma, an incurable hematological cancer. We aimed to provide foundational knowledge about patient experiences and healthcare providers' opinions and practices concerning care for MGUS patients in the United States.

**Methods**

We conducted semi-structured qualitative interviews to explore clinical experiences of patients with MGUS and to determine whether receiving an MGUS diagnosis influences patients' patterns of healthcare utilization in a sample of 14 patients recruited from ResearchMatch and Facebook. We also conducted semi-structured qualitative interviews with eight healthcare providers. Interviews were analyzed using thematic analysis.

**Results**

We identified a total of six overarching themes around the care pathway for patients with MGUS. The first theme (1) was related to the process of MGUS diagnosis. Providers saw MGUS

as an incidental and asymptomatic condition, while patients reported having symptoms, they considered to be related to MGUS. Three themes focused on the meaning of an MGUS diagnosis, relating to: (2) providers' explanation, (3) patients' understanding, and (4) the impact of the diagnosis. Overall, patients have a basic understanding of MGUS. However, some patients feel anxiety around the diagnosis, which may affect other aspects of their lives. The fifth (5) theme was related to follow-up/management. We found that patients primarily see hematologists for follow-up care; non-hematologist providers report having less specific knowledge about MGUS. The last theme (6) was related to factors influencing healthcare utilization. We found the most influential factors to be age, disease severity, and insurance/cost.

## **Conclusion**

Our findings suggest that some patients with MGUS may need psychosocial support services to help process their diagnosis with a premalignant condition. In addition, we identified gaps in knowledge around caring for MGUS patients among non-hematologist providers, and variation in MGUS follow-up practices. Finally, the factors identified to influence care for patients with MGUS are similar to factors influencing care for other chronic conditions.

## INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition characterized by elevated amounts of monoclonal protein (M-protein) present in the blood. MGUS is diagnosed more often in older adults and in men; however, cases are mostly asymptomatic and almost always diagnosed incidentally when patients seek care for other conditions.<sup>24,45,52</sup> It is estimated that nearly 3% of adults over 50 years old may have clinical evidence of MGUS,<sup>30,48-51,74</sup> yet the vast majority of these individuals remain undiagnosed. However, patients with MGUS can progress to more severe diseases, including the incurable hematological cancer multiple myeloma (MM), at a rate of approximately 1% per year.<sup>22,53 75</sup>

Previous studies have shown that patients with MGUS or smoldering myeloma, an intermediate condition between MGUS and multiple myeloma, exhibit similar psychological distress as patients with multiple myeloma.<sup>76</sup> A recent qualitative study from Ireland describes the poor psychological experiences that patients with MGUS endured during diagnosis and follow-up appointments due to uncertainty about potential progression to multiple myeloma.<sup>77</sup> Patients also reported experiencing isolation, poor information-provision and increased uncertainty after MGUS diagnosis.

Patients with MGUS experience frequent follow-up clinical visits in intervals ranging from three months to two years. There are four international clinical practice guidelines for MGUS, all based on expert consensus, yet their recommendations vary widely.<sup>26-29</sup> In the United

States (US), MGUS clinical surveillance practice patterns vary by sociodemographic characteristics; older patients are more closely followed than younger adults.<sup>32</sup> Geographic variation in follow-up patterns has also been observed, with patients in the Northeastern US followed-up less frequently than patients from any other US region.<sup>32</sup> In addition, the follow-up care for approximately half of patients with MGUS from a retrospective claims data analysis using the OptumLabs Data Warehouse diagnosed in 2013 lacked concordance with any of the existing recommended clinical practice guidelines.<sup>32,33</sup> Patients with multiple myeloma preceded by a known MGUS diagnosis have been observed to have better long-term survival than multiple myeloma patients without this prior diagnosis,<sup>24,52,69</sup> though mechanisms remain unclear.<sup>38,52,53</sup> The primary goal of this study was to understand the perspectives and experiences of patients with MGUS as well as the providers who diagnose and care for them. We also explored patient- and provider-level drivers behind patterns of healthcare services utilization.

## METHODS

### Research design

We conducted semi-structured one-on-one interviews with patients who had been diagnosed with MGUS to gain insight into their experiences and the factors that might influence their healthcare utilization practices before and after receiving an MGUS diagnosis. In addition, we conducted one-on-one semi-structured interviews with providers to understand the typical processes leading to an MGUS diagnosis and to explore potential provider-level drivers of health service utilization in addressing MGUS. All interviews were conducted through secure phone calls and recorded. This study was approved by the University of Massachusetts Medical School Institutional Review Board and all participants gave oral informed consent to participate.

### Study Participants and Settings

*Patients with MGUS:* Patients were recruited from MGUS-related support groups on Facebook and through the ResearchMatch database.<sup>78</sup> ResearchMatch and Facebook have previously been used to recruit patients for qualitative studies and studies of healthcare decision making.<sup>78,79</sup> All interested participants with MGUS were provided with a fact sheet describing the study. Inclusion criteria included a self-reported diagnosis of MGUS, aged between 18-80 years, and ability to speak English or Spanish, and ability to provide oral, informed consent

*Providers:* Healthcare providers were identified through the investigators' (MC, ME, KM) professional networks of healthcare providers at the University of Massachusetts Medical

School and Reliant Medical Group, both located in central Massachusetts. Inclusion criteria included healthcare providers who may treat patients with an MGUS diagnosis including but not limited to those in the fields of primary care, hematology/oncology, and geriatrics. Provider types included physicians, nurse practitioners, and physician assistants.

### **Interview content**

Interviewees were asked a series of open-ended questions. An experienced qualitative researcher helped to develop and revise interview guides (KM). We collected information on sociodemographic characteristics for all participants, including age, gender, race/ethnicity, years in practice and specialty (providers only), and state of residence (patients only). We gathered information from patient participants about their experiences with their MGUS diagnosis and perceptions of how this diagnosis has influenced their care. Among provider participants, we solicited their perspectives on why patients may be more likely or less likely to obtain specific health services (Interview guides).

### **Qualitative thematic analysis**

All interviews were transcribed and de-identified by the primary study investigator (MC). The coding process began with an unstructured read of the transcripts and familiarization with the data. After an initial review of the transcripts, we generated a preliminary list of codes.<sup>80,81</sup> The preliminary coding scheme was developed by the primary investigator, and reviewed by an experienced qualitative researcher (KM) and a cancer epidemiologist (ME). The preliminary coding scheme was applied to a subset of transcripts by all three investigators who then met to discuss coding, generate new codes as needed and refine code definitions. The primary



investigator applied codes to all the interviews (MC) and a second team member reviewed for accuracy (KM, ME). Memos of decisions were logged at each step of the planned coding process; team members met to review and discuss disagreements and modification of definitions. After all interviews were coded and collated, we reviewed coded responses and identified themes and subthemes. Patient and provider interviews were analyzed separately, and corresponding themes were compared (e.g., providers' views on how patients understand the MGUS diagnosis versus patients' descriptions of how they would explain the diagnosis).

## RESULTS

### Characteristics of the participants

A total of eight provider participants were interviewed; of those, five were female, four were non-Hispanic White, four were hematologists, four were non-hematologist providers, four had more than three years of medical practice, and four treat more than ten patients with MGUS in a year. All provider participants were currently practicing in Massachusetts (Table 6). A total of 14 patient participants with MGUS were interviewed; of those 10 (71.4%) were female, 11 (79.6%) were 70 years old or less, 10 (71.4%) were non-Hispanic White, and eight (57.1%) were living in the southeastern US. All patient participants had a bachelor's degree or higher, eight (57.1%) had lived for six or more years with a MGUS diagnosis, and 10 (71.4%) reported to have good or very good overall health. Patients with MGUS in this study reported having several comorbid conditions, including musculoskeletal diseases (e.g., arthritis, bone pain; N=7) (Table 7).

### Summary of themes

We identified a total six overarching themes among patient and provider participants that map onto the MGUS care pathway from diagnosis through follow-up. These themes include (1) process to MGUS diagnosis; (2) providers explanation of MGUS; (3) patients' understanding of MGUS; (4) impact of MGUS diagnosis; (5) follow-up/management; and (6) factors influencing healthcare utilization (Figure 2). These themes are described in detail below.

- 1. Process of MGUS diagnosis:** This theme included the process of clinical evaluation that led provider participants to an MGUS diagnosis and affected patient participants' experiences in healthcare encounters leading up to MGUS diagnosis.

*Circumstances leading to providers to evaluate for a possible MGUS diagnosis:* Provider participants reported that patients with MGUS are often incidentally diagnosed while being evaluated for another acute or chronic condition, though some diagnoses were found during routine lab workups.

*Patient participants' experiences during MGUS diagnosis:* In contrast to provider participant reports, six patient participants reported experiencing mostly nonspecific symptoms that led to the MGUS diagnosis including rash, itch, tingling, severe bone pain, fatigue and skin lesions. Patient participants reported a variety of experiences in receiving MGUS diagnosis. Five patient participants described empathetic providers who actively sought to identify (i.e., diagnose) the problem, took time to explain the diagnosis, and communicated with other providers on behalf of the patient. In contrast, two patient participants described physicians who they felt did not prioritize MGUS due to other concerns in their care. In addition, seven patient participants believed their provider did not have sufficient knowledge of MGUS, and so actively sought out more knowledgeable providers.

*“The person who diagnosed me with it didn't really know anything and he was like, at this point, all I can do is refer you to someone else and then you have to wait...then the person that I got*

*was more concerned about other issues. And so that took me a couple of years to find somebody that was specifically looking at [MGUS].” (Female, 5 years with MGUS)*

- 2. How providers explained MGUS to patients:** This theme includes how provider participants explained the MGUS diagnosis to their patients and what they should expect. We also included the challenges to explaining MGUS to patients that provider participants reported during this process in this theme.

***Providers’ explanations of MGUS:*** Provider participants’ reports of how they explain MGUS to their patients included two aspects: a medical description (e.g., “*a protein abnormally elevated*”) and reassurance of the common and usually non-harmful nature of the diagnosis, e.g., “*common finding as people gets older*”). Patient participants’ reports of their conversations with their providers were consistent with these findings.

***Providers’ explanations about what patients could expect after the diagnosis:*** Provider participants also reported that they gave patients information about what to expect with this diagnosis, including that: (1) MGUS has a risk of progression to multiple myeloma if M-protein rises; (2) elevation of M-protein could affect organ function (anemia, renal failure, high calcium, etc.); (3) MGUS is a chronic condition that needs close monitoring and, while there is no need to be concerned right now, follow up with a blood specialist is necessary to look for signs and symptoms of progression. Patient participants’ reports of their conversations with their providers were consistent with these findings.

**Challenges in explaining MGUS to patients:** In general, provider participants reported that they explained MGUS using simple language for all patients, regardless of literacy level or other factors. Three provider participants noted that MGUS is a condition that is difficult to explain. However, one provider participant mentioned they modify their description of MGUS based on perceived patient understanding, and two provider participants indicated the challenges of explaining MGUS to non-English speaking patients using an interpreter.

*“I think the explanation so much doesn't change. Sometimes with the interpreter use, I stick to my same kind of language, but I'm not really sure what the interpreter is saying. Like, how do they say abnormal protein? You know what I mean? And how do the patients perceive it? It can be almost impossible for me to know, the medical interpreters are qualified in translating medical terms. I'm hoping that they they're able to convey exactly what I have in mind.”*

*(Hematologist)*

- 3. Patient participants understanding of an MGUS diagnosis:** This theme includes patient participants' definition and understanding of the MGUS diagnosis and sources of information patients have used to find more information about MGUS.

**Patient participants' definitions:** Twelve patient participants were able offer an explanation of MGUS using definitions more ambiguous compared to those reported by providers, for example:

*“something funny in my blood that didn't cause any problem but can become something serious”*

*(Female, 16 years with MGUS)*

*“The best way I can explain it is that they don't know for sure. That's the reason it says unknown significance is not there for sure. The best way I can say if I was gambling, I would gamble at the fact that I have the possibility based upon my blood work says that I am more likely to have a lymphoma or something like that than the average person that does not have this in their genetic blood.” (Female, 15 years with MGUS).*

However, two patient participants reported they do not understand MGUS and hoped one day they can learn more about it.

**Sources of information:** All patient participants in this study used the internet to access information about MGUS, referring to medical journals and social media sites like Facebook. Social media, in particular, was helpful for some patient participants to share information and get recommendations to help with specific disease-related symptoms. One patient participant said:

*“I am on Facebook, I've been talking with, ... texting or messaging, different people who have MGUS and, definitely sharing information” (Female, 3 months with MGUS)*

One provider participant noted that patients have the potential to access unreliable information via the internet and that they may hear information from friends and family and then call the physician to clarify.

- 4. Impact of an MGUS diagnosis:** This theme includes provider participants' perspective on patients' responses as well as patient participants' reported emotional response and actions taken after the diagnosis.

***Provider participants' perspectives:*** Provider participants acknowledged that some patients may experience anxiety associated with this diagnosis, similar to other pre-cancerous conditions. Two provider participants reported offering reading materials or further discussion to clarify what to expect with an MGUS diagnosis when they perceive that a patient feels nervous or anxious. Provider participants mentioned the importance of reassuring patients, and that follow-up and subsequent healthcare utilization could be influenced by the patient's reaction. Provider participants also reported that the need to visit a hematology-oncology department could be inherently stressful for some patients and make them worried about having cancer.

***Patient participants' feelings or emotional responses:*** Patient participants reported varied responses to getting an MGUS diagnosis. Some reported relief after finding out they had MGUS and not something more serious like multiple myeloma or amyloidosis. One said:

*"I mean having MGUS seems like the better alternative to any other type of disease that could come from it". (Female, 3 months with MGUS)*

Three patient participants reported having a neutral response, such as:

*"I just feel fortunate that I'm able to continue on and realize that I have to live with it and take whatever comes." (Male, 6 years with MGUS)*

Other patient participants found the diagnosis mentally draining and reported that they were constantly thinking about it after the diagnosis:

*“I think anytime you get a diagnosis like that, you have anxiety. ... and when you have children, especially you worry about your own mortality and being alive to see them, ..., grow up and do things.” (Female, 10 years with MGUS)*

Finally, some patient participants recognized their emotions fluctuated, particularly when time came close to follow-up visits. One said:

*“The biggest impact that I’ve had is when it’s time for my appointments, where I, ... go for the blood tests about a week in advance ...when we get there to discuss the test results, then the biggest impact has been I get a little depressed”. (Female, 5 years with MGUS)*

***Actions taken by patient participants:*** Some patient participants reported taking actions after getting the diagnosis, including making changes to their insurance policy or taking herbal remedies. One patient participant was keeping a diary of skin changes while another patient reported getting married earlier than planned.

- 5. Follow-up and/or management plan:** This theme refers to the follow-up practices described among patient and provider participants in this study, including used of other healthcare services, and patient participants experiences during MGUS follow-up. Also, this theme identifies the need to establish the importance of MGUS follow-up

***MGUS follow-up practices:*** After an MGUS diagnosis, two patient participants were followed by their primary care physician while all others were followed by a hematologist. Providers reported variability in the specialty of providers responsible for patient follow-up with MGUS,



with non-hematologist mostly responsible for long-term surveillance. In general, hematologists saw the patient only to confirm the MGUS diagnosis, then referred them back to the primary care physician. However, two hematologist provider participants mentioned that they follow patients with MGUS if the patient needs more reassurance or if the primary care physician does not feel comfortable managing these patients. One provider participant mentioned patients with MGUS are followed by multiple providers, and two other provider participants mentioned the primary care physician and hematologist collaboratively manage patient's care. One provider participant highlighted the need for increased knowledge about MGUS among primary care physicians:

*“So the one thing about MGUS, it's kind of like an incidental finding... sometimes we get more of these patients that we should be getting. What would really be helpful is education of primary care physicians of what it means and when they need to worry about that.” (Hematologist)*

In contrast to provider participant reports, 12 patient participants reported being followed-up by a hematologist rather than a primary care physician, as the latter were not familiar with the condition.

The frequency of clinical follow-up done by the provider participants was variable, ranging from every three months to every two years. Some provider participants indicated the frequency of follow-up depends on laboratory test results and patient risk level. Provider participants noted the lack of clear follow-up guidelines for following patient participants with MGUS:

*“So we see them, ... every six months, sometimes every 12 months, ... there is no real guidelines, different organization or different country has its own set of rules. ...there's such a variability into how often you need to check them.” (Hematologist)*

Even though most standard surveillance tests (e.g., serum protein electrophoresis) were mentioned by almost all the providers, differences in the frequency of testing were reported. For example, immunofixation tests may not be ordered routinely because a positive result won't change over time:

*“I don't routinely do immunofixation because immunofixation has already been done and it should be positive going forward.” (Hematologist)*

***Mental health services and other services:*** Most provider participants reported that there are no specific health services needed by patients with MGUS. However, if patients are experiencing specific symptoms (e.g., neuropathy), they may receive relevant treatment (physical therapy). Provider participants also mentioned that in general patients with MGUS generally do not need referrals to mental health services. Oncologist provider participants expressed confidence in their ability to reassure patients, provide information, and communicate with family members. However, one provider participant reported that while patients with MGUS may not need a referral to mental health services, they may need such a referral later if their condition progresses to multiple myeloma.

Patient participants may feel differently about this, as one patient mentioned the importance of checking on patients' emotional wellbeing:

*“As much, and as passionate as physicians are... there is not often the time to say, can we do a little check-in? How are you doing emotionally and intellectually so that we can understand that part to treat the whole person instead of just the condition.” (Female, 14 years with MGUS)*

***Patient participants' experiences during MGUS follow-up:*** Patient participants reported difficulty finding a provider with adequately familiarity with MGUS. One patient participant traveled out of state each year to continue follow-up with a provider comfortable with MGUS. In addition, one patient participant highlighted how providers play an important role in the follow-up of patients:

*“The people who treat you make an enormous difference in how this goes”. (Male, 10 years with MGUS)*

***Follow-up importance:*** Patient participants reported the need to understand the importance of MGUS follow-up:

*“You really have to have a mental construct about ... why would you take time out of your day to do this thing? it's not something that's causing you any problems, why should you do anything?” (Female, 16 years with MGUS)*

One patient, who developed multiple myeloma after 16 years with MGUS described how knowing the importance of follow-up would be helpful:

*“What difference does it make? ... what will happen if ... it emerges into illness, I will get treated, you know, and they would say, well, if we catch it a little earlier, it will be a little better.” (Female, 16 years with MGUS)*

**6. Factors influencing healthcare utilization:** All providers participants indicated they continue the same management plan and generally do not alter the care of MGUS patients. One provider participant mentioned that the factors influencing healthcare

utilization after an MGUS diagnosis are no different than for other chronic conditions.

However, patient and provider participants both reported a few factors that can influence healthcare utilization. Some of those were:

***Symptoms/comorbidities:*** Provider participants mentioned that any signs of progression, such as neuropathy or renal insufficiency, and/or patients with high risk MGUS (IgM subtype) will result in more aggressive follow-up, where a short life expectancy or advanced comorbid disease result in less aggressive MGUS follow-up. Provider participants may change MGUS follow-up practices if patients have comorbidities. In general, patients with poorer overall health were less likely to prioritize monitoring for MGUS progression.

***Patient age:*** Provider participants varied in whether they modified their follow up care based on patient age. Some providers indicated that age influenced clinical follow-up patterns, with older patients receiving less intense follow-up than younger patients. In contrast, other provider participants indicated that MGUS follow-up is not age-dependent while others still expressed conflicting thoughts on the influence of age.

In addition, one patient participant commented that she felt she was getting less attention, given her young age:

*“It tends to get kind of pushed off.... You're young. You don't really need to worry about medical issues yet.” (Female, 5 years with MGUS)*

***Other barriers/factors influencing healthcare utilization:*** Other factors influencing healthcare utilization that were identified by patient and provider participants included: providers' lack of knowledge of MGUS can lead to unnecessary referrals; patients' interest in having more frequent

follow-up; patient feelings, like anxiety/worry; family history of multiple myeloma; transportation concerns; emotional and physical burden; COVID-19 related concerns; language barriers; insurance/cost; distance from home to healthcare facilities; the difficulties and monotony of enduring long term follow-up; and waiting time for lab results. One patient participant said:

*“I certainly spend a lot more money on copays and certain things that aren't covered. And it does put financial stress” (Male, 6 months with MGUS)*

## **DISCUSSION**

This study provides insights into patients and providers' experiences with MGUS and patterns of MGUS follow-up healthcare utilization. The providers and patients who participated in this qualitative study expressed emphasized the importance of different aspects of follow-up care. We described patients' experiences with an MGUS diagnosis and follow-up care to understand how they view an MGUS diagnosis and integrated it into regular care that they sought out. We identified these themes: (1) process to MGUS diagnosis; (2) providers explanation of MGUS; (3) patients' understanding of MGUS; (4) impact of MGUS diagnosis; (5) follow-up/management; and (6) factors influencing healthcare utilization.

### **MGUS diagnosis, follow-up and management**

Studies have shown that cancer patients have better outcomes if they have greater utilization of primary care before diagnosis.<sup>40-43</sup> Primary care generally plays a central role in the delivery of healthcare delivery system and serves as the basis for building a strong healthcare system that ensures better health outcomes and health equity.<sup>82</sup> Patients with MGUS seem to have frequent follow-up visits to monitor their disease,<sup>25</sup> which may be a direct result of established guidelines and recommendations. However, in our study we found that the majority of patients are followed by a hematologist-oncologist, due to the lack of MGUS knowledge among primary care physicians. This gap in primary physician knowledge could delay a newly diagnosed patient's referral to hematologist-oncologist or incur in additional specialty referrals as a patient rules out other conditions.

Previous studies have observed that patients with multiple myeloma preceded by a known MGUS diagnosis have better long-term survival than multiple myeloma patients without this prior diagnosis,<sup>24,52,69</sup> though the reasons for this remain unclear.<sup>52,53,75</sup> Investigating healthcare utilization by patients with MGUS may provide insight into the mechanisms behind the improved survival of multiple myeloma patients with this preceding diagnosis.<sup>39,83</sup> A previous study that evaluated the follow-up practices of MGUS in the US found that MGUS follow-up practice patterns varied geographically and demographically and were frequently discordant with guideline recommendations.<sup>25</sup>

A recent study from a cohort of patients with MGUS living in southeastern Minnesota and followed up at Mayo Clinic, examined the indications for monoclonal protein testing, subsequent diagnoses made, and follow-up practice patterns.<sup>84</sup> They found monoclonal protein testing is commonly performed for signs and symptoms not typically associated with lymphoplasmacytic malignancies. In addition, there was significant variation in MGUS follow-up between hematologists and non-hematologists that is not based on risk factors or clinical practice guidelines.<sup>84</sup> Similar to our study, providers and patients reported variations in follow-up practices. There is the need for clear and consistent recommendations for MGUS surveillance to reduce the potential for miscommunication and ensure adequate follow-up for all MGUS patients. In particular, patients in our study indicated the importance of recognizing the benefit of continuous, long-term follow-up for a condition that does not often cause any urgent medical concerns.

### **Providers' explanation and patients understanding of MGUS**

A previous study has found that physicians describe MGUS to their patients using simple terminology such as “abnormal protein” and using analogies that the patient was more likely to be familiar with, such as comparing a paraprotein to the finding of a mole or lump.<sup>44</sup> Also, education level, age and cognitive ability are found to be important factors in deciding how and whether information was relayed to patients.<sup>44</sup> However in our study, providers indicated that they generally give the same definition to all patients. Also, providers recognize that MGUS is difficult to explain, and it is challenging to explain the condition to those patients who need interpretive services.

A previous study that investigated patients' knowledge and understanding of nonmalignant blood disorders found that patients may understate the significance of such conditions.<sup>37</sup> In contrast, almost all patient participants in our study seemed to understand MGUS, although a few patients recognized that they do not have a good understanding of the condition.

### **Impact of MGUS diagnosis**

We found that providers recognized that patients with MGUS could present with anxiety associated with MGUS diagnosis and long-term follow-up. However, providers also expressed confidence that they were able to reassure patients, educate them, and communicate with family members, and were not likely to refer patients to mental health resources. Patients expressed different emotions after an MGUS diagnosis, including anxiety, which may affect other aspects of their lives. These results suggest an unmet need for providers to evaluate the emotional well-being of MGUS patients, and possibly make mental health resources more available. These



observations are similar to a qualitative study of patients with MGUS in Ireland, which found that an MGUS diagnosis can result in isolation and increased uncertainty.<sup>77</sup>

### **Study Strengths and Limitations**

This study had several strengths including the evaluation of both patient and providers' perspectives of MGUS. However, we recognize this study does have several limitations. First, we recruited a relatively small number of patients, and the use of ResearchMatch and/or social media for recruitment may limit the generalizability of the results, as our participants may be more educated or engaged than typical patients. In addition, our patient participants were mainly non-Hispanic White patients and highly educated. The patients who were interviewed were unlikely to have been cared for by the providers in the study; thus, future research exploring differences in perceptions within patient-provider dyads would be useful. Finally, given the small number of providers interviewed we were unable to make comparisons across specialties.

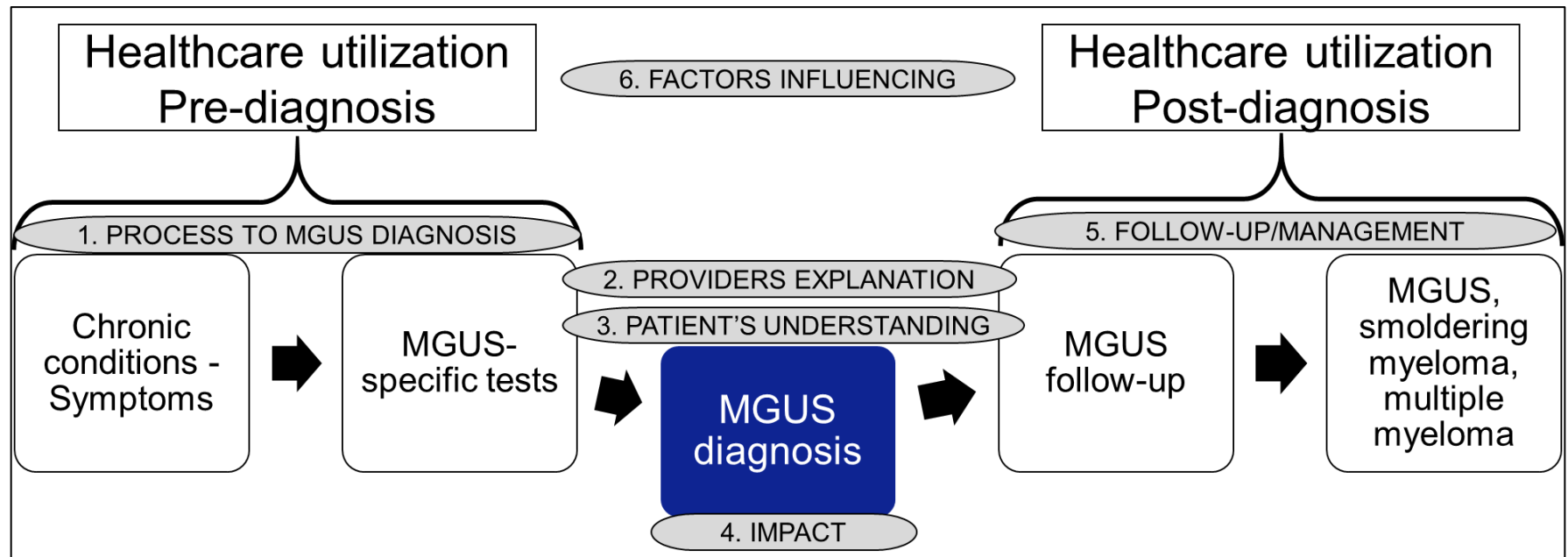
### **Conclusion**

Future studies should explore strategies for increasing primary care providers' knowledge and self-efficacy in MGUS management, as was suggested by patients' reports of difficulty finding physicians who could offer adequate follow-up care. These findings also suggest that providers should screen for and address mental health concerns more often among patients with MGUS. Providers should be aware that an MGUS diagnosis may negatively impact a patient's mental health and should be prepared to offer adequate mental health referrals if needed. In summary, these findings are an important first step in understanding patients' experiences with

MGUS, as well as patient and provider-level drivers of healthcare utilization related to a diagnosis of MGUS.

**TABLES AND FIGURES**

**Figure 2.** Overarching themes identified among patients and providers around healthcare utilization before, during, and after diagnosis of monoclonal gammopathy of undetermined significance (MGUS)



Overarching themes – gray ovals

**Table 6.** Self-reported characteristics of US medical providers who care for patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS)

Characteristics	Providers	
	N=8	
	N	(%)
<b>Gender</b>		
Male	3	37.5
Female	5	62.5
<b>Race/ethnicity</b>		
Non-Hispanic White	4	50.0
Asian/Indian	4	50.0
<b>Type of provider</b>		
Non-hematologist	4	50.0
Hematologist	4	50.0
<b>Years of practice</b>		
≤ 2	4	50.0
3-10	2	25.0
≥ 11	2	25.0
<b>Practice setting</b>		
Private practice	2	25.0
Hospital	6	75.0
<b>Number of patients with MGUS seen per year</b>		
≤ 10	4	25.0
11-20	2	25.0
≥ 21	2	25.0

**Table 7.** Self-reported characteristics of patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS)

Characteristics	Patients with MGUS	
	N=14	
	N	(%)
<b>Gender</b>		
Male	4	28.6
Female	10	71.4
<b>Age</b>		
≤60	3	21.4
61-70	8	57.1
≥71	3	21.4
<b>Race/ethnicity</b>		
Non-Hispanic White	10	71.4
Non-Hispanic Black	2	14.3
Multi-racial	2	14.3
<b>Region of residence</b>		
Northeast (MA, NY)	2	14.3
Southeast (NC, FL, VA, MS, KY, TN)	8	57.1
Midwest (IL, IN)	3	21.4
West (CA)	1	7.1
<b>Level of education</b>		
Doctoral degree	3	21.4
Master's degree	4	28.6
Bachelor's degree	7	50.0
<b>Any family history of cancer</b>	11	78.6
<b>Years since MGUS diagnosis</b>		
≤ 1	2	14.3
2-5	4	28.6
6-10	3	21.4
≥ 11	5	35.7
<b>Comorbid conditions at time of interview*</b>		
Neuropathy	1	7.1
Diabetes	2	14.3
Kidney disease	2	14.3
Hypertension	4	28.6
Musculoskeletal disorders	7	50.0

\* mutually exclusive

**CHAPTER V:**

**DISCUSSION AND CONCLUSIONS**

## CHAPTER V: DISCUSSION AND CONCLUSIONS

### SUMMARY OF FINDINGS

The main goal of this dissertation was to provide a foundation of knowledge for future studies of healthcare utilization among patients with MGUS. Specifically, this research was designed to assess factors contributing to healthcare utilization in a population diagnosed with a prevalent yet understudied premalignant condition, with the intention of laying a foundation for future studies that will help elucidate potential targets to improve the long-term health and survival of patients with MGUS.

Using data from a community-based provider group in central Massachusetts, **the first study aimed** to describe relevant MGUS biomarkers' (creatinine and hemoglobin laboratory values) trajectories during a period of three years after MGUS diagnosis, as these are monitored for disease progression. We identified three distinct groups of patients with MGUS sharing similar trajectories of creatinine and hemoglobin laboratory values over the three years following diagnosis. Slightly more than half of the patients with MGUS had a normal creatinine and hemoglobin trajectory, while 44.3% of patients had a trajectory with lower hemoglobin levels that remained within the range of normal. Lastly, a smaller group of patients (2.6%) had a trajectory characterized by high creatinine and borderline low hemoglobin levels. We found that few patients in our study population transitioned to multiple myeloma over the course of our study.

**Our second aim** consisted of a matched cohort analysis of patients seeking care at a large provider group in central Massachusetts. We examined whether a diagnosis of MGUS was associated with differences in ER, hospital, and outpatient visits compared to patients without an MGUS diagnosis. We found that patients with MGUS had higher rates of ER, hospital, and outpatient visits one year before and after, as well as during the two-month period around MGUS diagnosis/index date. However, different patterns of utilization were observed between the different time intervals. Patients with MGUS had higher rates of hospital visits than patients without MGUS one year before, and during the two-month period around MGUS diagnosis/index date. However, the rates of ER and outpatient visits were higher than patients without MGUS during the two-month period around the MGUS diagnosis/index date.

The **final study aim** explored the patient- and provider-level drivers of healthcare utilization in patients with MGUS. The providers and patients who participated in this qualitative study expressed varied opinions regarding MGUS follow-up and healthcare utilization. We described patients' experiences with an MGUS diagnosis and follow up to understand how patients view their MGUS diagnosis in context of their overall care. Overall, patients demonstrated a basic understanding of MGUS and its implications. However, some patients reported feeling anxiety associated with an MGUS diagnosis, which may affect other aspects of their lives. In contrast, providers saw MGUS as an



asymptomatic and incidental diagnosis that does not cause any trouble and indicated that patients did not need additional healthcare services (e.g., mental health referrals). Finally, providers viewed the factors influencing MGUS management strategy are generally no different than those that affect the management of other chronic conditions. Furthermore, we found that primary care providers may require additional and specific training on MGUS to ensure adequate follow-up care of these patients.

### **STRENGTHS AND LIMITATIONS**

The research conducted for this dissertation has several notable strengths. We conducted a population-based analysis of the multiple myeloma precursor MGUS using both quantitative and qualitative methods. The findings reported in the three studies presented here will add knowledge to the relatively scarce literature on the impact of receiving an MGUS diagnosis on healthcare utilization. This study is the first to evaluate healthcare utilization pre- and post-MGUS diagnosis, as well as compared to a population without MGUS (matched cohort design), in a community-based sample of patients with MGUS with longitudinal electronic health record data. For the first two studies of this dissertation, we used a database of patients with MGUS diagnosed between 2007 to 2015 who were identified with an innovative algorithm based on electronic health data, with a portion of cases validated through EHR review.<sup>85</sup> We used a rigorous advanced statistical method (group-based trajectory modeling) to conduct an innovative analysis to disentangle how levels of two common clinical biomarkers evolve over time prior to and following the diagnosis of MGUS and identified distinct groups of patients based on these clinical markers. Finally, this study was the first to evaluate the drivers of healthcare utilization in patients with MGUS at both the patient and provider levels using qualitative methods.

We also recognize that this work had several limitations. Because the majority of MGUS cases are undiagnosed, the study findings are generalizable to all patients with

diagnosed MGUS, which by definition requires access to medical care. Since the algorithm used to detect patients with MGUS was developed in the setting of a healthcare delivery system, the findings for the first two analyses may be limited to an insured population. Electronic health data offer several challenges including missing data, missing variables, and variability in the amount of data available in the EHR per patient, including MGUS-related surveillance testing. Advanced analytic approaches (e.g., multiple imputations for missing data) were applied to address these challenges. We acknowledge that we could not completely compensate for data missing in patients' EHR (e.g., smoking status, alcohol used, and body mass index). Regarding the qualitative study, we performed a relatively small number of interviews with patients and providers, and there may still be themes left to be explored. However, this approach should be sufficient to learn about the range of ideas and to inform new different hypotheses to explore in future quantitative and mixed methods studies. Also, the patients who were interviewed may not have been cared for by the providers who participated. Future studies may investigate patient-provider dyads. Finally, given the small number of providers interviewed, we were unable to make comparisons across specialties.

## **FUTURE RESEARCH**

The work produced from this dissertation has provided foundational information on healthcare utilization among patients with MGUS. However, future research is still needed. There are several areas that future studies should examine in relation to biomarker trajectories of patients with MGUS. First, additional laboratory value trajectories including M-protein and calcium levels should be examined. The inclusion of additional laboratory results will provide a more comprehensive picture of patients with MGUS and their pathway towards potential progression to multiple myeloma. Second, future studies should include diverse populations, especially those known to be at a higher risk of multiple myeloma, such as African Americans to determine if biomarker trajectories are similar in other populations, and to increase generalizability of findings. It is important to note that our study sought only to characterize MGUS patients based on biomarker trajectory, and not to predict risk of progression to multiple myeloma. Additional methods must be developed to further apply identified trajectories to risk prediction.

Future studies evaluating comorbid conditions related to MGUS diagnosis and follow-up are needed to understand the differences in healthcare patterns observed among patients with MGUS, since the differences observed could be related to other conditions and not due to MGUS diagnosis. Additional research is also needed to understand the mechanisms behind healthcare utilization in patients with MGUS, including in larger and more diverse populations of patients with validated MGUS diagnoses. Given the

limitation that our participants were mainly identify as non-Hispanic White, our results may lack generalizability. Future work in this field should also incorporate a greater number of diverse geographical locations given known geographic variation in follow-up practices in the US. Future studies may explore additional healthcare services, such as preventive health behaviors, that could help us better understand the overall health and care patterns of patients with MGUS.

Lastly, results from our qualitative analysis of patients with MGUS suggest that future studies must evaluate the need of patients with MGUS to be monitored by primary care physicians with adequate knowledge for emerging signs of multiple myeloma progression. Lack of adequate follow-up among patients with MGUS could result in a greater risk of MGUS patients having avoidable complications. Our study identified potential gaps in training as primary care providers may not be adequately informed on care for patients with MGUS. As such, future studies may develop educational materials not only for primary care providers, but also for newly diagnosed MGUS patients to inform themselves on the disease. If primary care providers lack adequate knowledge around the importance of regular surveillance or possible complications from MGUS, patient symptoms may be inadequately evaluated.

## CONCLUSION

This dissertation has evaluated the influence of receiving a diagnosis for the precancerous condition MGUS in relation to healthcare utilization practices. MGUS is the precursor of multiple myeloma, one of the most common forms of hematological cancer, with five-year survival rate of just 54%<sup>86</sup> despite recent improvements in treatment. MGUS and multiple myeloma are more common among adults aged 50 years and older and people of African descent who have a 2-fold higher risk than non-Hispanic White patients. The goal of this dissertation was to shed light on this understudied premalignant condition and its impact on healthcare utilization, as well as characterize subgroups of patients based on commonly measured biomarkers and gain a better understanding of patient- and provider-level drivers of health behaviors in this population. Future research should further investigate how the group trajectories identified in this study may be related to the risk of progression to multiple myeloma, including evaluating the addition of biomarkers such as M-protein levels. In addition, we suggest that an MGUS diagnosis is associated with higher utilization of ER, hospital, and outpatient visits, especially during the months surrounding the diagnosis date. Our study suggests the need for additional psychosocial support services for patients with MGUS who may experience anxiety as a result of the diagnosis. There should also be a focus on enhancing primary care provider education on MGUS follow-up.

Although MGUS is asymptomatic and incidentally diagnosed, there appear to be several characteristics, both biological and behavioral, that distinguish this patient population from patients without an MGUS diagnosis. The findings of this dissertation work shed light on this understudied premalignant condition and its impact on healthcare utilization, as well as identify patient- and provider-level drivers of health behaviors in this population.

**APPENDICES:**

**SUPPLEMENTAL FILES BY CHAPTER**

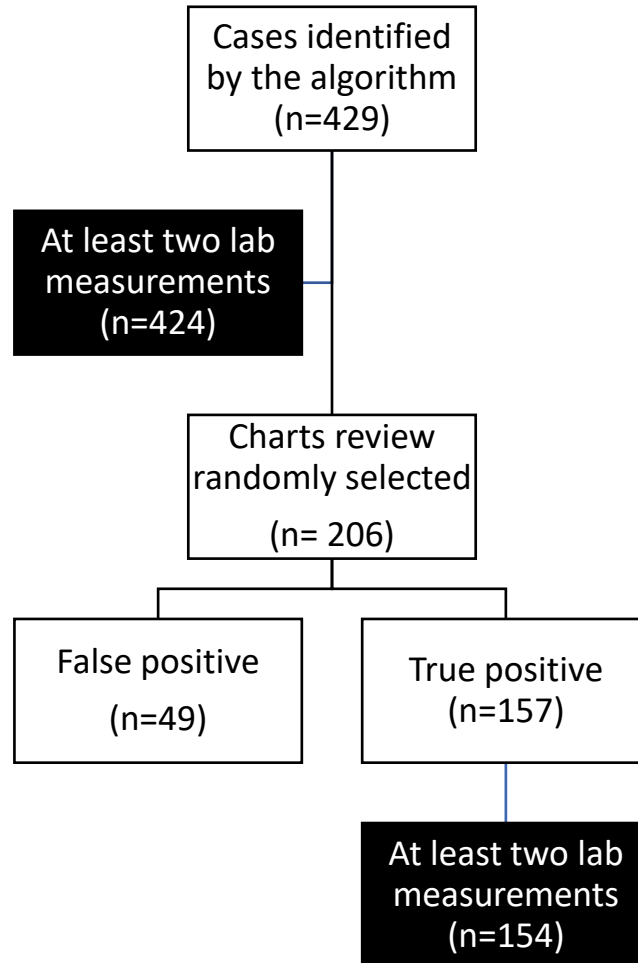


## SUPPLEMENTAL MATERIAL CHAPTER II

Castañeda-Avila MA et al. Multi-Trajectory Models of Serum Biomarkers among Patients with Monoclonal Gammopathy of Undetermined Significance. *Cancer Epidemiology Biomarkers and Prevention*

<b>Supplemental figure/table</b>	<b>Description</b>
<b>Supplemental Figure 1.</b> Flow chart cases of MGUS identified by the algorithm	Final sample size use in the main manuscript and the sensitivity analysis.
<b>Supplemental Table 1.</b> ICD-9 and ICD-10 codes used to calculate the Charlson Comorbidity Index among MGUS cases diagnosed 2007-2014.	ICD codes used to calculate the Charlson Comorbidity Index score in the year before the MGUS diagnosis date.
<b>Supplemental Table 2.</b> Sociodemographic and clinical characteristics at MGUS diagnosis of patients with MGUS diagnosis validated (n=154)	Sensitivity analysis sample - sociodemographic characteristics of participants.
<b>Supplemental Figure 2.</b> Three multi-trajectories of creatinine and hemoglobin fitting lines (n=154)	Sensitivity analysis sample - Group trajectories identified
<b>Supplemental Table 3.</b> Baseline characteristics by predicted trajectory group (n=154)	Sensitivity analysis sample -Differences in patient characteristics among patients with validated MGUS diagnosis by varying biomarker trajectories

**Supplemental Figure 1.** Flow chart cases of MGUS identify by the algorithm.



**Supplemental Table 1.** ICD-9 and ICD-10 codes used to calculate the Charlson Comorbidity Index among MGUS cases diagnosed 2007-2014.

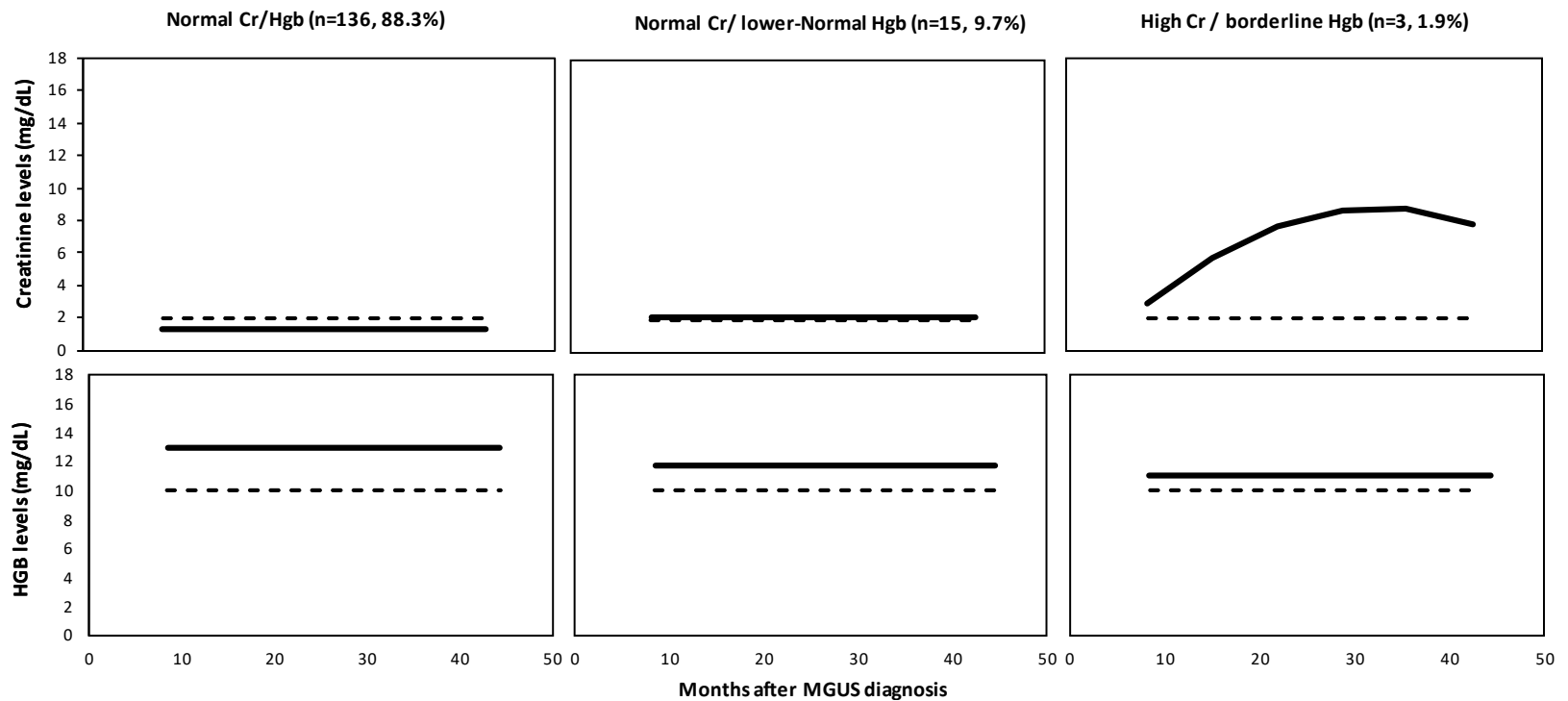
<b>Conditions</b>	<b>ICD-9</b>	<b>ICD – 10</b>
Myocardial infraction	410-410.92, 412	I21-I22.9, I25.2
Congestive heart disease	428-428.9	I50-I50.999
Peripheral vascular disorder	440.20-440.24, 440.31 440.32, 440.8, 440.9, 443.9, 441-441.9, 785.4, V43.4, V43.4	I70-I71.9, I73.01, I73.1, I73.9, I79.0, I96, Z95.8-Z95.9
Cerebrovascular disease	430-438.9	G45-G46.999, I60-I69.999
Dementia	290-290.9	F00-F03.999, F05-F05.999
Chronic pulmonary disease	490-496, 500-505, 506.4	J40-J47.999, J60-J67.999, J68.4
Rheumatologic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725	M05-M06.999, M32-M34.999, M35.3
Peptic ulcer disease	531-534.91	K25-K28.999, K56.60
Mild liver disease	571.2, 571.5, 571.6, 571.4-571.49	K70.0-K70.31, K73-K74.999, K75.4
Diabetes	250-250.33, 250.7-250.73	E10.10-E10.11, E10.51-E10.52, E10.59, E10.641, E10.65, E10.69, E10.9, E11.00 - E11.01, E11.51-E11.52, E11.59, E11.641, E11.65, E11.69, E11.9, E13.00-E13.01, E13.10-E13.11, E13.51-E13.52, E13.59, E13.641, E13.9
Diabetes with chronic complications	250.4 -250.63	E10.2-E10.5, E10.61-E10.619, E11.2-E11.5, E11.61-E11.619, E13.2-E13.5, E13.61-E13.619
Hemiplegia or paraplegia	344.1, 342-342.92	G04.1, G81-G82.999
Renal Disease	582-582.9, 583-583.7, 585-586, 588-588.9	N03.0-N03.9, N05.2-N05.5, N05.9, N06.2 -N06.5, N07.2-N07.5, N08, N17.1-N17.2, N18.1-N18.6, N18.9, N19, N25.0, N25.1, N25.81, N25.89, N25.9
Malignancy, including leukemia and lymphoma	140-172.9, 174-195.8, 200-208.91	C00-C26.999, C30-C34.999, C37-C41.999, C43-C43.999, C45-C45.7, C46-C58.999, C60-C76.999, C81-C85.999, C86-C86.999, C88-C88.999, C90-C97.999, D03.0, D03.10-D03.12, D03.20-D03.22, D03.30, D03.39, D03.4, D03.51-D03.52, D03.59, D03.60-D03.62, D03.70-D03.72, D03.8, D03.9, D45
Moderate or severe liver disease	572.2-572.8, 456.0-456.21	I85.00-I85.01, I85.10-I85.11, K70.41, K71.11-K72.01, K72.10-K72.11, K72.90-K72.91, K76.6 -K76.7
Metastatic solid tumor	196-199.1	C45.9, C77-C80.999
AIDS	042-044.9	B20-B20.999

**Supplemental Table 2.** Sociodemographic and clinical characteristics at MGUS diagnosis of patients with an EHR-validated MGUS diagnosis

<b>Characteristic</b>	<b>Patients with MGUS (n=154)</b>
<b>Men, n (%)</b>	78 (50.6)
<b>Age at index date (Mean ± S.D.), years</b>	75.6 ± 10.3
<b>Race, n (%)</b>	
Non-Hispanic White	131 (99.2)
Non-Hispanic Black	1 (0.8)
<b>Socioeconomic index, n (%) <sup>a</sup></b>	
Low	35 (39.3)
Medium	27 (30.3)
High	27 (30.3)
<b>Tobacco use, n (%)</b>	
Never	51 (36.2)
Current smokers	19 (13.5)
Quit/Former/Passive Smokers	71 (50.3)
<b>Current alcohol use, n (%) <sup>b</sup></b>	56 (46.7)
<b>Body mass index, n (%)</b>	
Underweight (<18.5 kg/m <sup>2</sup> )	4 (3.1)
Normal (18.5-25 kg/m <sup>2</sup> )	38 (29.7)
Overweight (25-30 kg/m <sup>2</sup> )	43 (33.6)
Obese (≥30 kg/m <sup>2</sup> )	43 (33.6)
<b>Previous cancer diagnosis, n (%) <sup>c</sup></b>	
Breast (among women)	4 (5.3)
Prostate (among men)	5 (6.4)
Other	4 (2.6)
<b>Charlson comorbidity index, n (%) <sup>d</sup></b>	
0	45 (29.2)
1	27 (17.5)
≥ 2	82 (53.2)
Mean ± SD	2.2 ± 2.2
<b>Mean serum Cr levels, (± S.D.), mg/dl <sup>e</sup></b>	1.3 ± 0.9
<b>Mean serum Hgb levels, (± S.D.), mg/dl <sup>f</sup></b>	12.6 ± 1.4

May not total 100% due to rounding. Cr=creatinine; Hgb= Hemoglobin. Missing values: Race (n=22), socioeconomic status index (n=65), tobacco (n=13), alcohol (n=34), body mass index (n=26) <sup>a</sup> Tertiles of factor score of median household income, median house rent, percentage of the population living below 150% of the poverty line, education index, and percent unemployed; <sup>b</sup> Current vs never; <sup>c</sup> presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis; <sup>d</sup> Using a modified Charlson score with 15 components; <sup>e</sup> Normal levels less than 2mg/d; <sup>f</sup> Normal levels between 12 and 15 mg/dl

**Supplemental Figure 2.** Three multi-trajectory groups of creatinine and hemoglobin values defined among 154 validated cases of MGUS in central Massachusetts.



The dotted-line (----) represents the cut-off point for the definition of abnormal values for each biomarker. Renal insufficiency is defined as creatinine (Cr) levels >2 mg/dl. Anemia is defined as hemoglobin (Hgb) levels <10 mg/dL.

**Supplemental Table 3.** Characteristics at MGUS diagnosis by predicted trajectory group

Characteristic	Normal Cr/Hgb	Normal Cr/ Lower-normal - Hgb	High Cr/ borderline Hgb
<b>Total, n (%)</b>	136 (88.3)	15 (9.7)	3 (1.9)
<b>Men, n (%)</b>	66 (48.5)	10 (66.7)	2 (66.7)
<b>Age at index date (Mean ± S.D.), years</b>	75.7 ± 10.5	74.3 ± 9.7	77.7 ± 6.9
<b>Race, n (%)</b>			
Non-Hispanic White	120 (99.2)	9 (100)	2 (100)
Non-Hispanic Black	1 (0.8)	0	0
<b>Socioeconomic index, n (%)<sup>a</sup></b>			
Low	32 (39.5)	2 (28.6)	1 (100)
Medium	23 (28.4)	4 (57.1)	0
High	26 (32.1)	1 (14.3)	0
<b>Tobacco use, n (%)</b>			
Never	46 (36.8)	4 (30.8)	1 (33.3)
Current smokers	15 (12.0)	3 (23.1)	1 (33.3)
Quit/Former/Passive Smokers	64 (51.2)	6 (46.1)	1 (33.3)
<b>Current alcohol use, n (%)<sup>b</sup></b>	53 (48.2)	3 (37.5)	0
<b>Body mass index, n (%)</b>			
Underweight (<18.5 kg/m <sup>2</sup> )	4 (3.4)	0	0
Normal (18.5-25 kg/m <sup>2</sup> )	37 (31.6)	1 (11.1)	0
Overweight (25-30 kg/m <sup>2</sup> )	38 (32.5)	4 (44.4)	1 (50.0)
Obese (≥30 kg/m <sup>2</sup> )	38 (32.5)	4 (44.4)	1 (50.0)
<b>Previous cancer diagnosis, n (%)<sup>c</sup></b>			
Breast (among women)	4 (5.7)	0	0
Prostate (among men)	5 (7.6)	0	0
Other <sup>b</sup>	2 (1.5)	1 (6.7)	1 (33.3)
<b>Charlson comorbidity index, n (%)<sup>d</sup></b>			
0	42 (30.9)	3 (20.0)	0
1	27 (19.8)	0	0
≥ 2	67 (49.3)	12 (80.0)	3 (100)
Mean ± SD	1.9 ± 2.0	3.8 ± 2.8	5.0±3.0
<b>Serum Cr, (Mean ± S.D.), mg/dl<sup>e</sup></b>	1.1 ± 0.3	2.2±0.4	6.1±3.8
<b>Serum Hgb, (Mean ± S.D.), mg/dl<sup>f</sup></b>	12.7 ±1.4	11.7 ± 1.0	11.1 ± 1.0

May not total 100% due to rounding. Cr=creatinine; Hgb= Hemoglobin. Missing values: Race (n=22), socioeconomic status index (n=65), tobacco (n=13), alcohol (n=34), body mass index (n=26) <sup>a</sup> Tertiles of factor score of median household income, median house rent, percentage of the population living below 150% of the poverty line, education index, and percent unemployed; <sup>b</sup> Current vs never; <sup>c</sup> presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis; <sup>d</sup> Using a modified Charlson score with 15 components; <sup>e</sup> Normal levels less than 2mg/d; <sup>f</sup> Normal levels between 12 and 15 mg/dl

## SUPPLEMENTAL MATERIAL CHAPTER III

**Supplemental Table 1.** Current Procedural Terminology codes of healthcare services evaluated, and services used to define MGUS follow-up.

<b>Healthcare service</b>	<b>CPT Codes</b>
<b>Emergency department visits</b>	99281, 99282, 99283, 99284, 99285
<b>Hospital visits</b>	99221, 99222, 99223, 99238, 99239
<b>Office or outpatient visits</b>	99201-99205, 99211- 99215, 99241- 99245, 99386, 99387, 99396, 99397

## SUPPLEMENTAL MATERIAL CHAPTER IV

### INTERVIEW GUIDES

#### INTERVIEW PROTOCOL FOR PROVIDERS

*This document is to be used as a discussion guide during the interview session. It should not be used verbatim as a questionnaire. The questions and probes may be used differently depending on the participant feedback and level of comfort with the process. The interviewer may ask probing or follow up questions to more fully explore or clarify issues brought up on a given question or over the course of the entire interview.*

#### Welcome

**Intent:** The goal of section 1 is to greet the participant, explain the study and obtain verbal consent.

- Greeting the participant: *“Hello, my name is \_\_\_\_\_ and I will be talking with you about MGUS”*.
- Thank the participant for taking the time to participate in our study: *“Thank you very much for being a part of this study and taking the time to speak with me today”*
- Explain the study: *“Just as a reminder, our goal is to understand how a diagnosis of MGUS affects healthcare utilization”*
- Review informed consent and obtain verbal consent
- Explain that we will be audio-recording the interview so we can gather more information from their stories later.  
*“First, we need to complete the consent process. I’d like to record this interview if that’s ok with you. We will store the de-identified transcript on our password protected computer.”*
- Inform participant that recorded data is in no way linked to the study subject and that we will not be using their name in the recording



- Ask participant to refrain from using names – particularly names of patients – during the recording
- Initiate recording “*I am now turning on the recorders.*”
  - Turn on recording.
  - Begin the recording by stating the date and time.
  - Confirm permission to record the encounter.

*“This is subject ID number 001 and the interview date is April XX, 2020”*

### **Experiences with MGUS**

- So you are [fill in what you believe to be their role – e.g., primary care physician]?  
Is that right?
- And how long have you been in practice?
- Tell me about your experience with patients with MGUS. About how many patients with MGUS do you see in a year?
- And how do you take care of these patients? What, if anything, do you do for patients with MGUS due to that diagnosis?
- Probe: Do you have a specific patient management plan for patients with MGUS?
- Do you recommend certain screenings or other testing related to MGUS surveillance?
- How much does your approach or your management strategy vary across patients with MGUS?
  - Probe: How does your care of one patient with MGUS differ from your care of another patient with MGUS?
  - What factors influence your management strategy for your patients with MGUS?

### **Factors that may influence healthcare utilization**

- In general, do you see patients with MGUS having more or different needs for healthcare compared to patients of similar age, gender, background who don’t have MGUS? What differences, if any, do you see?

- It's my understanding that MGUS is more common amount adults aged 50 and older. Does patient age affect how you care for patients with MGUS?
- What about patient sex? Does that affect your management plan?
- Could you describe to me how a MGUS patients' level of education may impact the care you offer?
  - How would you explain the condition (MGUS) to someone with a low health literacy level?
- What preventative, diagnostic, or general healthcare services do you think are most important for patients with MGUS?
  - Do you think patients with MGUS need any special counseling due to their diagnosis?
  - What kinds of emotional responses and issues related to coping have you seen in MGUS patients? Have any required additional mental health referrals? (probe for details)
- What barriers do you think exist to providing those services? On the provider, clinic or system side? On the patient side?
  - Do you think a MGUS patient's social networking, support networks, family, and friends, influence their own healthcare utilization? (probe for details)
  - How do you think health insurance status affects the care provided to patients with a MGUS diagnosis?
  - What aspects of a patient's overall health status and need for medical care affect service utilization in patients with MGUS? (Probe for details)

### **Closing and follow up**

We are about to end the interview. Is there anything you'd like to add about how you care for patients with MGUS? Or their needs for or use of healthcare services related and unrelated to MGUS?

Do you have any questions for me?

Thank you for talking with me. I'm going to shut off the recorder now.

**TURN OFF RECORDER.**

I appreciate all the information and feedback you have given me. Your answers will help us understand the healthcare utilization of patients with MGUS.

- Thank the provider for their valuable contribution to this research.
- Immediately after the interview (after you have left the participants' area or ended the phone interview), write down any general reflections about the interview, thoughts about the participants attitudes or reactions, or any other potentially pertinent info.

**Demographic Data Sheet**

**Subject ID:** \_\_\_\_\_  
\_\_\_\_\_

**Date:**

**Race/ethnicity**

- American Indian/Alaska Native
- Asian
- Black/ African American
- Hispanic or Latino
- Native Hawaiian/Pacific islander
- White
- Other

**Gender:**

- Male  Female  \_\_\_\_\_

**Years in Practice:** \_\_\_\_\_

**Type of provider:**

- Nurse practitioner

Primary care physician

Oncologist

Other \_\_\_\_\_

## **INTERVIEW PROTOCOL FOR PATIENTS**

*This document is to be used as a discussion guide during the interview session. It should not be used verbatim as a questionnaire. The questions and probes may be used differently depending on the participant feedback and level of comfort with the process. The interviewer may ask probing or follow up questions to more fully explore or clarify issues brought up in a given issue, or over the course of the entire set of interviews.*

### **Welcome**

**Intent:** The goal of section 1 is to greet the participant, explain the study and obtain verbal consent.

- Greeting the participant: *“Hello, my name is \_\_\_\_\_ and I will be talking with you today about MGUS.”*
- Thank the participant for talking the time to participate in our study: *“Thank you very much for being a part of this study and taking the time to be here today”*
- Explain the study: *“As a reminder from the materials you’ve seen already, the purpose of this interview is to enable us understand what it is like to be diagnosed with MGUS, and how that affects your healthcare, for example, how often you see your doctor and what tests have been done”*
- Review informed consent and obtain verbal consent
- Explain that we will be recording the interview, so we can gather more information from their stories later.

*“First, I want to be sure that you understand what we are doing and that your privacy will be protected. This interview will be recorded. All data will be stored on our secure, password protected computer. The recording of our conversation today will be transcribed and analyzed. Your personal information will not be*

*included, and only the people working on this study will be able to see or hear what you say.”*

- Inform participant that their name will not be included in the recording or transcript
- Ask participant to refrain from using their own name and/or the real names of others during the recording

*“There are no right or wrong answers. Please respond according to what applies to you and if there is any question that you prefer not to answer, please let me know and we can move on to the next question. Do you have any questions before we begin?”*

- Initiate recording *“I am now turning on the recorders.”*
  - Turn on the two recorders.
  - Begin the recording by stating the date and time.
  - Confirm permission to record the encounter.

*“This is subject ID number 001 and the interview date is April XX, 2020”*

### **Experiences with MGUS and overall health**

- First, I’d like to understand a bit about your current health. How would you describe your overall health?
  - Do you have any medical problems or conditions that are concerning to you? Or that interfere with your day to day life?
- Now I’d like to hear about what it was like for you to be diagnosed with MGUS.
  - When were you first told that you have MGUS?
  - Tell me about how you were diagnosed.
  - Did you have any symptoms at that time?
  - What was it like for you to receive that diagnosis?
  - How was MGUS first described to you? What were you told about MGUS?

- If you were to explain what it means to have MGUS to someone who had never heard of it, how would you explain it?
- Has this diagnosis had an impact on your day to day life?
- Has this diagnosis affected your ability to do the things you want to do or need to do?
- Can you tell me how you feel about your MGUS diagnosis?
  - So you were diagnosed about [x months/years] ago. What has it been like for you over the past x time?
  - Do you feel worried about your MGUS diagnosis?
  - (*If yes, ask*) How might this fear affect when you decide to go to the doctor? (whether you go more because of this scare – or do you avoid the doctor?)
  - What does a MGUS diagnosis mean to you? – can you tell me more about that?

#### **Factors that may influence healthcare utilization**

- Have you tried to find information on MGUS, no including healthcare providers (like doctors, nurses, etc)? [if yes, then continue]
- Where have you looked, or who have you asked for information? Have you done any research on the internet? Tell me about what sort of research you have done. What kinds of information were you looking for? And were you able to find what you needed?
- Now I am going to ask about treatment and medical care.
- Tell me about how this diagnosis has changed – or not changed – your healthcare. By healthcare I mean what medications you take, how often you see a doctor, what doctors you see, and what tests you have done, such as imaging scans or blood tests.
- Have you had any treatments for MGUS specifically?
- Has having a diagnosis of MGUS affected any treatments you might have for other conditions?
- Have you had any additional testing related to having MGUS after being diagnosed?
- Have you made any changes in the providers you see for your healthcare since your diagnosis?

- Are there services or types of care that you use more since your diagnosis?  
Tell me about more about that.
  - Are there services that you stopped using or are using less since your diagnosis?
- There are a lot of things that affect whether and how people get healthcare. What do you think influences whether and how you get care?
  - What about MGUS? How much does this diagnosis influence the care you receive?
  - Do you have other chronic conditions that require frequent doctor visits or tests?
  - Any other health services that you use for chronic conditions?
  - What factors like family, work, etc do you think may affect the quality of care for patients with MGUS?
- How does your current income influence the care you seek or receive as a patient with MGUS? Tell me more about this.
- How does your health insurance status affect the care you receive as a patient with MGUS?
- How does your medical provider affect the care you receive as a patient with MGUS?
- Do you think your social network, including family and friends, influence your use of healthcare services?
- How does your social support network affect how you use healthcare services? Do you use more or fewer health services because of this support?
- Has your social support network always been the same? Or has it changed since the MGUS diagnosis?
- Do you believe your age and/or sex has an effect on the healthcare services you use?
- In what ways does your race or ethnicity affect the overall healthcare you have received after your MGUS diagnosis?

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- Could you describe how your education level may impact your overall healthcare since you were diagnosed with MGUS?

### **Closing and follow up**

We are just about done. Do you have anything else you would like to say about what it's like to have MGUS? Or about your interactions with healthcare providers and the healthcare system in general?

Do you have any questions for me?

Thank you for participating in this interview. I'm going to shut off the recorder now.

### **TURN OFF RECORDER.**

Thank you again for talking with me! It's been very helpful.

- Immediately after the interview (after you have left the participants' area or ended the phone interview), write down any general reflections about the interview, thoughts about the participants attitudes or reactions, or any other potentially pertinent information.

### **Demographic Data Sheet**

**Subject ID:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**How do you identify yourself in terms of race and ethnicity?**  American Indian/Alaska Native

Asian

Black/ African American

Hispanic or Latino

Native Hawaiian/Pacific islander

White



APPENDICES

Other

**And in terms of Gender:**

Male  Female  \_\_\_\_\_

**What is the highest level of education you completed:**

Some high school

High school graduate

Some college

Associate degree

Bachelor's degree

Graduate school

Doctorate/professional degree (\_\_\_\_\_)

**Family History:**

Has anyone in your immediate family been diagnosed with any of the following conditions (e.g., parents, siblings, children)

Multiple myeloma if yes, who?

Smoldering myeloma if yes, who?

Other cancer diagnosis if yes, who?

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