MGUS: A Journey in Time
A Long-term Follow-Up of 1384 Patients

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We identified 1384 patients residing in Southeastern, Minnesota, in whom MGUS was diagnosed at the Mayo Clinic from 1960-1994. The primary endpoint was progression to multiple myeloma or a related disorder. The 1384 patients were followed for 14,488 person years (median 25.2 yrs), range 0-43 years during which 1289 (93%) died. During follow-up, multiple myeloma (MM) developed in 97 patients with 4.0 expected with a relative risk of 24.0 fold (19-29); lymphoma 19 (expected 11.5), relative risk 1.7 (1-2.6); AL amyloidosis 14 (expected 1.6), risk 8.6 (5-14). Waldenstrom's Macroglobulinemia (WM) 13 (expected 0.27) with a relative risk of 48 fold (26-82). The cumulative probability of progression to one of these disorders was 10% at 10 years, 18% at 20 years and 27% at 30 years and 37% at 35 years. The overall risk of progression was about 1% per year and most importantly patients were at risk for progression even after 30 years or more of stable MGUS. The cumulative incidence of death due to other diseases including cardiovascular and cerebrovascular diseases and non-plasma cell malignancies were 56% at 10 years, 79% at 20 years and 87% at 25 years compared with 7% at 10 years, 10% at 20 years and 11% at 30 years for death due to plasma cell malignancies. Patients with MGUS had a shorter survival than expected for Minnesota residents of matched age and sex (median _8.1 years_ vs _12.0 years years) ($p < 0.001$). The number of patients with progression to a plasma cell neoplasm or related disorder (147) was more than 6 times expected on the basis of incidence rates for those conditions in the general population. The 97 patients with MM constituted 66% of the 147 patients who progressed to a plasma cell malignancy. Multiple myeloma was diagnosed more than 10 years after the detection of the MGUS in 42 of

the 97 patients (43%), after 20 years of follow-up in 16 patients (16%), and in 3 patients after 30 years of follow-up in 3%. Multivariate analysis revealed that the size of the M spike, type of heavy chain (IgG vs IgA or IgM), abnormal FLC ratio and presence of splenomegaly were significant features for risk of progression.