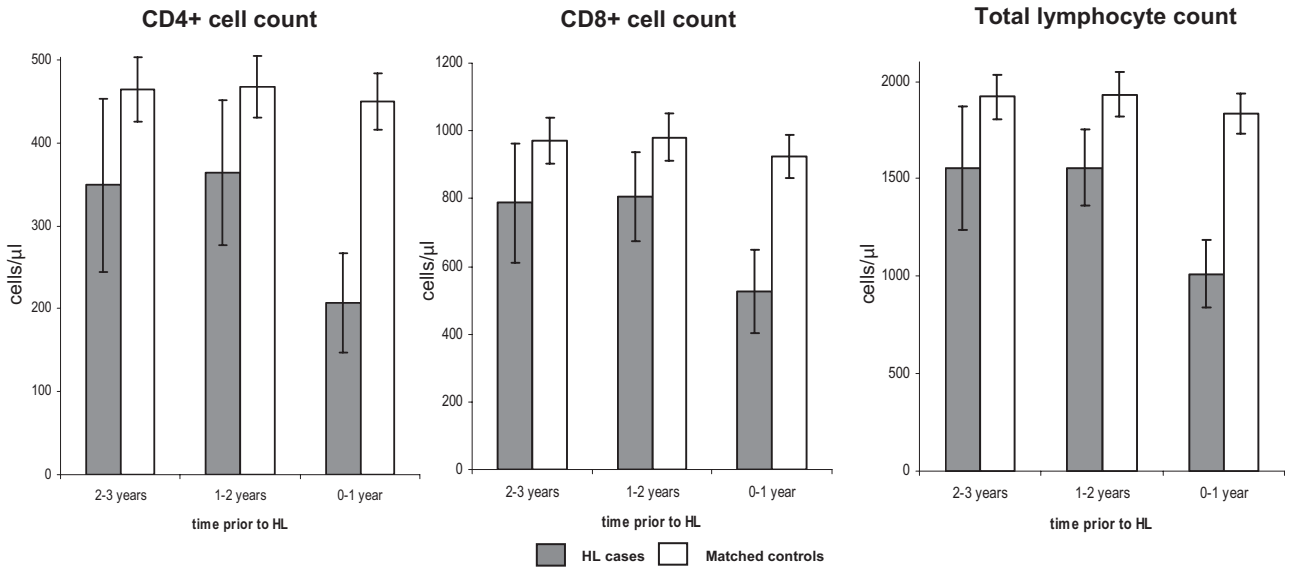

Figure 1. Trends in CD4$^+$ cell, CD8$^+$ cell, total lymphocyte counts and 95% confidence intervals, by time prior to HL diagnosis among 26 HL cases and 202 matched controls.[3]

We agree with Dolcetti et al that other cohorts of closely followed HIV-infected persons, with assessment of CD4$^+$ and CD8$^+$ cell counts at multiple time points with respect to HL diagnosis should be evaluated to clarify these issues. Ideally, EBV-specific CD4$^+$ and CD8$^+$ cell counts might also be assessed.

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The Swiss HIV Cohort Study (SHCS) has been approved by the ethical committees of all the collaborating clinics and the present analysis was additionally approved by the scientific committee of the SHCS and the ethics committee of the International Agency for Research on Cancer (IARC). Written informed consent was obtained from all SHCS participants in accordance with the Declaration of Helsinki.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

A monoclonal gammopathy in search of clinical significance: 57 years later

The articles by Landgren et al and Weiss et al published in a recent issue of *Blood* provided incontrovertible evidence that all multiple myelomas are preceded by monoclonal gammopathy of undetermined significance (MGUS).[1,2] While this association is expected, the findings are important and further strengthen the biologic significance of MGUS. What remains unclear and perhaps the most important question at the moment is the clinical significance of MGUS when there is yet no treatment that can prevent its progression to myeloma. Several clinical questions urgently beg answers.

First, do myeloma patients with a preceding diagnosis of MGUS have a better outcome in terms of survival and major complications (fractures and dialysis-dependent renal failure) compared with those who don't? This needs to be addressed due to the high prevalence of MGUS (5.3% among age $\geq$ 50 years) and its low likelihood of progression (0.4%/year).[3,4] There are potential harms or disadvantages of indefinitely following MGUS. While comprehensive quality-of-life studies in MGUS are not available, the psychological burden of cancer anticipation can be disturbing. A preliminary study from our group showed that patients seen at our hematology clinic had similar degrees of psychological distress during follow-up visits regardless of whether the hematologic condition was benign or malignant. The distress level was the same among patients with MGUS and myeloma.[5] Moreover, the health care costs of following MGUS can be considerable. Based on the US Census Bureau, we calculated the number of patients harboring MGUS to be at least 3.6 million.[6] Assuming that only 25% are diagnosed, there would still be almost a million patients to follow annually. This is confounded by the fact that there is a projected shortage of 2550-4080 hematologists-oncologists by 2020.[7]

Second, assuming there is clinical benefit, what is the optimal way of following MGUS? Experts recommend annual follow-up with monitoring of monoclonal protein (M-protein).[8,9] However, we do not know if subsequent development of myeloma is generally detected at the time of scheduled follow-ups or in-between these appointments when patients present with symptoms. If the latter were true, this would argue against routine follow-up. In both studies by Landgren et al and Weiss et al, half of the patients who developed myeloma had relatively stable M-protein and none were high risk according to the Mayo Clinic model.[1,2] Therefore, monitoring of M-protein may be less important than once thought. Perhaps surveillance for *CRAB* signs (hypercalcemia, renal failure, anemia, and bone lesions) may be more useful. After all, treatment is not indicated in smoldering myeloma.

Finally, should clinicians use a higher threshold when ordering tests to look for monoclonal gammopathy? MGUS is by definition and clinical intention almost always an incidental finding. One could argue that every MGUS diagnosed is a failed clinical diagnosis of multiple myeloma and related disorders. Routine screening for MGUS is not indicated.

Since its first description by the Swedish hematologist Jan Gosta Waldenström in 1952, the clinical significance of MGUS remains to be determined.[10]

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Response

Multiple myeloma is universally preceded by a prolonged premalignant stage: novel clinical insights and future directions

Go and Doyle address important clinical questions based on our recent study showing that multiple myeloma (MM) is universally preceded by a prolonged premalignant stage.[1] Although the questions raised are not directly related to our paper, which focused primarily on a key biologic question, they are commonly encountered in clinical practice and worth discussing.

Routine screening for MGUS is not indicated. Therefore, almost all individuals diagnosed with MGUS represent incidental cases diagnosed when physicians order a serum protein electrophoresis and/or immunofixation as part of the workup of several common symptoms and laboratory abnormalities. Once diagnosed, patients must be appropriately counseled that MGUS is a premalignant entity with a relatively low risk of progression to MM or related malignancies. In fact, MGUS cases with small (< 1.5 g/dL) IgG monoclonal (M)–proteins and with a normal serum free light chain ratio, represent approximately 40% of all cases, and have only a 2% lifetime probability of developing MM or related malignancies. We have previously recommended that such MGUS cases may not need annual follow-up, but can rather be followed if symptoms suggestive of MM or related disorders occur.[2] In contrast, we feel that MGUS cases with higher risk may benefit from annual follow-up of the M-protein in addition to their usual medical care. Although the value of this is not proven, the test is simple, and, in our opinion, worth doing considering that MM can present with devastating bone complications that may be preventable in some patients if a significant rise in the M-protein is detected in time.

Although, for the individual patient, it is currently not possible to predict whether the underlying MGUS will remain benign or transform to MM, from a population standpoint the significance of MGUS has been well characterized. Several studies have determined the risk of transformation of MGUS patients over time,[3,4] and identified risk factors for such transformation.[2,5] In addition to malignant transformation, MGUS patients also have a higher risk of several pathologic conditions, including fractures[6] and deep vein thrombosis.[7] Furthermore, recent data suggest that MGUS cases (compared with the general population) have a significantly reduced life expectancy and an excess risk of dying from bacterial infections and heart, liver, and renal diseases,[8] although this may be related to the various underlying medical conditions that led to the detection of the MGUS. Additional clinical and epidemiologic studies of MGUS are needed.

Our recent observation that MM is universally preceded by a prolonged premalignant stage, with up to 75% of MM patients having detectable M-protein 8 or more years before diagnosis of the malignancy, fills a key gap in the present literature on myelomagenesis.[1] Simultaneously, we found that stable M-protein or free light chain levels do not exclude the development of MM