What about (MG)US? Towards tailored testing in monoclonal gammopathies

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In this issue of *Haematologica*, Chen and co-workers examine the multitude of challenges around monoclonal gammopathies with their numerous clinical facets.[1] These gammopathies include malignant diseases such as multiple myeloma (MM) as well as exceedingly rare conditions, for instance POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) syndrome, glomerulopathies, and skin disorders.[2] Most likely, the fate of a given individual diagnosed with a monoclonal gammopathy of undetermined significance (MGUS) (note the "undetermined") is, in fact, actually determined by an array of variables. The challenge for a physician when encountering an M spike on an electropherogram is to anticipate whether the underlying clone will remain stable ("true" or "benign" MGUS), develop towards a disease with a malignant phenotype or evolve into one of the rare disorders with devastating end-organ damage. Genetic alterations as well as differential usage of immunoglobulin variable genes have a significant impact on the phenotype and the longitudinal behavior of plasma cell diseases.[3-5]

Much work has gone into the analysis of genomic and transcriptional changes occurring during the evolution from early to advanced and symptomatic stages of plasma cell diseases.[3,4,6] Very recently, a group from the USA published their insights into how different genetic subtypes of smoldering multiple myeloma (SMM) predispose to specific progression dynamics and clinical outcomes.[6] The authors identified six subgroups that rely on different gene enrichments. They were able to identify three SMM groups at high risk of progression to active MM. These findings may guide future attempts at early interception (particularly in the three high-risk categories) with differential approaches depending on dysregulated molecular and oncogenic networks.[6]

Given the enormous expense required for sequencing technologies and bioinformatics, such comprehensive analyses are not yet ready for clinical-scale use. This is why, for the time being, clinical stratification models are important. These cover two areas of interest: first, the identification of populations who are at high risk of having MGUS or SMM and, second, the characterization of subjects with evolving SMM in whom the initiation of systemic therapy prior to the development of overt MM will be beneficial. While a first true population-based screening study is underway but still far from its readout,[7] there is clear evidence to support targeted screening in known high-risk groups. The incidence of MGUS is as high as 25% in black people aged 50 years or older who have at least one family member with MM. This incidence was also found in people with a different ethnic background aged 50 and older if at least two family members were diagnosed with MM.[8] Such a screening approach could result in placing subjects with high-risk SMM (still defined by clinical and laboratory parameters) on systemic therapy to prevent end-organ damage due to symptomatic MM. With many studies examining novel combinations of therapy still underway, there is some evidence that treatment with lenalidomide and dexamethasone in high-risk MM prolongs progression-free and overall survival when compared to observation only.[9]

A further layer of complexity in monoclonal gammopathies is the existence of very rare, non-malignant, albeit severely disabling entities, such as light-chain amyloidosis or renal, neurological or myopathic disease for which the abbreviation "MGCS" (monoclonal gammopathy of clinical significance) was coined.[2] These entities are typically characterized by their underlying low-burden plasma cell dyscrasias and by a broad spectrum of clinical symptoms. This highlights the need for more sensitive laboratory tests with respect to both confirming the presence of a monoclonal gammopathy and monitoring treatment response. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry has the potential to identify even small amounts of monoclonal proteins that go unrecognized by serum protein electrophoresis and serum immunofixation. A large study has proven its superiority in detecting monoclonal gammopathies in a defined screening

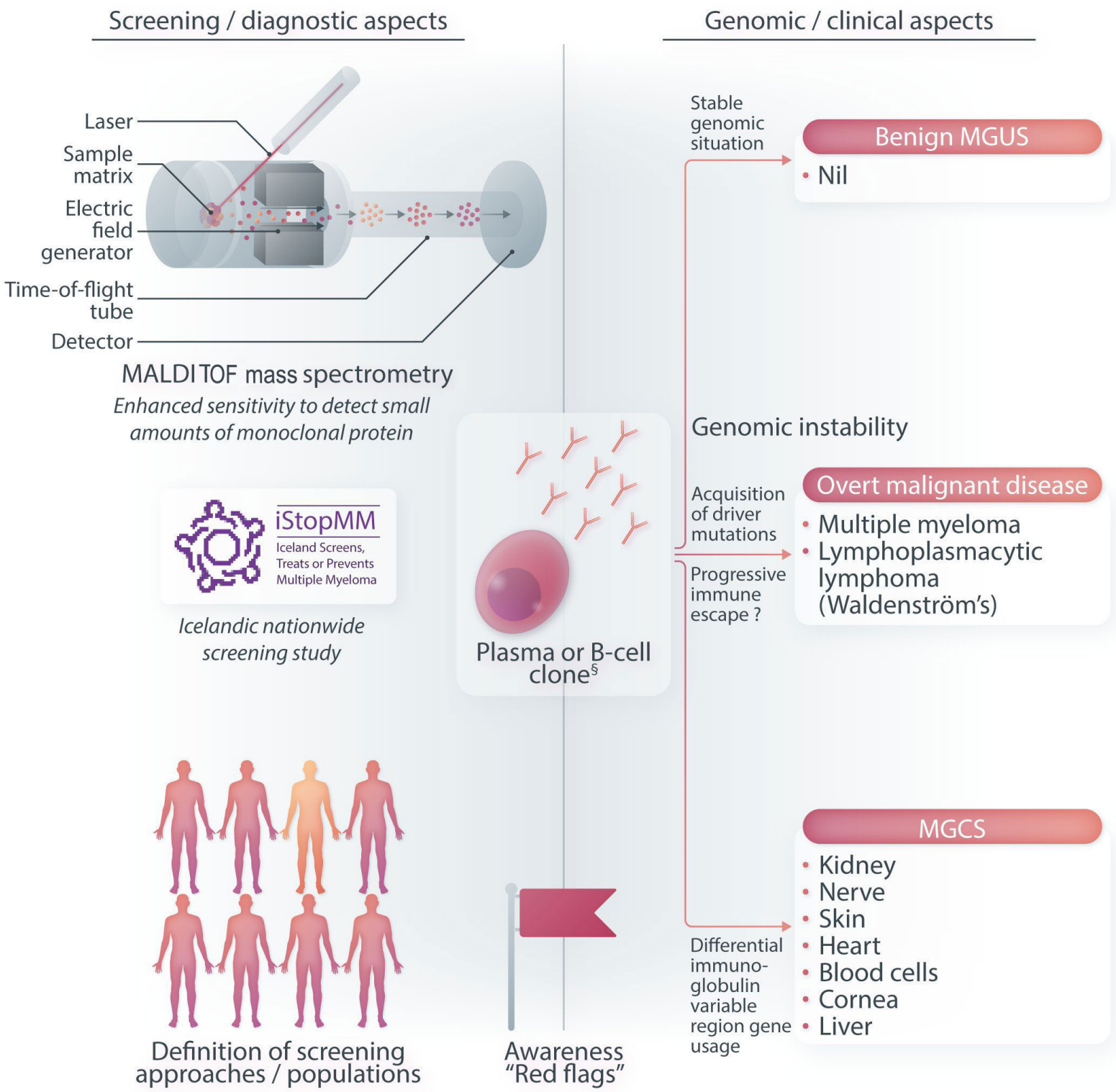

Figure 1. Considerations regarding diagnosis and surveillance of clonal B-cell/plasma-cell diseases. MALDI-TOF: matrix-assisted laser desorption/ionization-time of flight; MGUS: monoclonal gammopathy of undetermined significance; MGCS: monoclonal gammopathy of clinical significance.

cohort.[10] Mass spectrometry could in the future replace serum immunofixation, resulting in greater accuracy in detecting gammopathies and excluding false-positive cases on immunofixation. The incremental benefit of this advanced technology is most likely to occur in low-level conditions. From a diagnostic perspective, certain "red flags" may serve as initial clues to the underlying clonal B-/plasma cell proliferation. Awareness is a prerequisite to allow for a timely diagnosis.

In conclusion, a complex and clinically significant spectrum of disease takes center stage in the review by Chen *et al.*[1] The authors touch on all topics that are currently under debate: the question of whether screening for the "pre-symptomatic" condition is justified; the different mechanisms contributing to organ damage; the importance of early recognition of a monoclonal gammopathy; and the dilemma over how to establish the best screening algorithm. The review is an important contribution to the field and will certainly attract the interest of readers.

Disclosures

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Contributions

FB and SK wrote the manuscript and both authors approved its final version.

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