Definitive diagnosis of myelodysplastic syndrome (MDS) in a patient with cytopenias relies on demonstration of characteristic morphologic changes or MDS-defining cytogenetic abnormalities. However, many patients have a normal karyotype and lack the most distinctive pathologic features of MDS, such as ring sideroblasts or an excess of myeloblasts. In such cases, it may be difficult to exclude or establish a definitive diagnosis, and a degree of diagnostic variability has been recognized. The term “idiopathic cytopenia of undetermined significance” (ICUS) describes a broad category of patients with persistent unexplained cytopenias that do not meet criteria for MDS. As a diagnosis, however, ICUS has been known to inspire a measure of frustration, or even the rare obscenity, among clinicians.

Recent studies have established an important paradigm: a sizeable fraction of patients with ICUS have MDS-associated somatic mutations, and these patients may share genetic and clinical characteristics with those who have bona fide MDS.2,3 However, the natural history of patients with clonal versus nonclonal cytopenias has not been demonstrated, and evidence to guide clinical practice has been scant.

Malcovati et al evaluated mutations in a panel of 40 genes in a prospective cohort of 683 patients who presented for clinical evaluation of unexplained cytopenias and validated their findings in an independent cohort. On the basis of independent pathologic review, patients were determined to have myeloid neoplasm, ICUS, or “other” cytopenia. As was expected, most patients with myeloid neoplasms harbored canonical myeloid mutations, whereas these mutations were much less frequent in patients with ICUS or other cytopenias. Both the number of somatic mutations and the size of the mutant clone, as inferred from the variant allele fraction, had significant predictive values for myeloid neoplasm. However, there was marked heterogeneity in the clinical characteristics of specific mutations. For example, some mutations had high predictive value for myeloid neoplasm irrespective of co-occurring mutations, including those affecting RNA splicing (SF3B1, SRSF2, SFB3I), JAK2, and RUNX1. Others, such as mutations in TET2, DNMT3A, or ASXL1, had low predictive value unless paired with additional mutations. These results are highly consistent with data showing that somatic TET2, DNMT3A, and ASXL1 clones are commonly found in the blood of aging individuals and may require cooperating genetic events to cause development of clinically apparent myeloid malignancies.4,5

Using these mutation patterns, Malcovati et al asked whether patients with ICUS could be segregated by molecular profile into groups with distinct outcomes or likelihood of clinical progression. They found that patients with clonal ICUS had a much higher rate of progression (14-fold higher) than did patients with nonclonal ICUS. Importantly, they further showed that patients with clonal ICUS defined by highly specific mutation profiles had similar clinical characteristics to those with low-risk MDS patients, including older age, male bias, overall survival, and risk of disease progression. Somatic mutation status has not yet been substantively integrated into the latest revision to the World Health Organization (WHO) classification scheme.6 However, these findings should incite active discussion about whether the presence of highly specific mutation patterns in patients with ICUS provide presumptive evidence of bona fide MDS, even in the absence of definitive morphologic findings.

In contrast, does a negative molecular test have value in the evaluation of unexplained cytopenias? Many patients with unexplained cytopenias never develop a myeloid neoplasm. Prospective identification of this group of low-risk patients, who may need less invasive diagnostic testing and a more limited follow-up strategy, could reduce health care expenditures and provide more peace of mind for patient and physician. Malcovati et al show that the absence of somatic clonal mutations, particularly when paired with standard cytogenetic analysis, have a high negative predictive value. Similarly, patients with “mild” dysplastic changes and a negative mutation panel had exceptionally good outcomes, even though they formally fulfilled WHO morphologic MDS criteria. The predictive value of a negative test was enhanced by analyzing more genes, suggesting that there is utility in expanding the breadth of diagnostic gene panels.

Together, these findings have clear clinical implications, especially in the large population of patients with ICUS or MDS with mild dysplastic changes. However, several questions remain about how to fully integrate these findings into clinical practice. What is the role of bone marrow examination in the evaluation of unexplained cytopenias? Does a negative test obviate the need for a bone marrow study? Can a diagnosis of MDS be made without morphologic examination? How would prognostic models, such as the Revised International Prognostic Scoring System, be affected by refinement of MDS diagnosis to include MDS-defining mutation profiles? Future studies with ever-longer follow-up in longitudinal studies with comprehensive genetic annotation will be necessary to address these questions. At a minimum, staging of presumptive MDS by bone marrow
examination remains the standard of care and is a clinical imperative for patients who are considering treatment.

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Now I cuss less about ICUS

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