To the editors:

We read with interest the report of *Kristen et al.*, wherein the prognostic utility of histologic 'amyloid load' quantification by endomyocardial biopsy was described.(1) While the authors state that no significant variation was observed between biopsy sites, this observation was not quantified. Our collective experience is that Congo red staining of different biopsy specimens from within the same organ in the same patient can vary greatly in so called 'amyloid load', reflecting the patchy nature of amyloid deposition which is well described,(ref) and introduces the likelihood of sampling error. Furthermore, quantification of amyloid load from a single slide does not control for variation in sample size, as a true load would require normalization to total heart size determined by myocardial mass. In addition, immunohistochemistry in AL amyloidosis is associated with both 'false negative' and considerable background 'non-specific' staining calling into question the accuracy of quantification of amyloid burden by the method decribed. As the authors found no survival advantage with chemotherapy in AL amyloidosis in the context of higher levels of amyloid load (>20%), we are concerned that clinicians may choose to withhold life extending chemotherapy treatment from patients with advanced cardiac AL amyloidosis because of perceived futility, when it remains clear that some such patients do undoubtedly benefit from it. Cardiac MR with extra cellular volume (ECV) determination is an attractive non-invasive modality through which to quantify amyloid burden because the entire heart is imaged, yielding a truer average that has been shown to strongly correlate to cardiac specific biomarkers such as NT-proBNP.(2) Importantly, CMR with ECV measurement also lends itself readily to repeat measurements, has none of the attendant risks

of an invasive procedure, and is likely to afford a more sensitive means to follow amyloid regression with treatment.(ref abstract from ISA). We agree with the authors that precursor protein identification is an essential step in management of cardiac amyloid patients, and that endomyocardial biopsy has a definite role both in diagnosis and typing of cardiac amyloid. We would strongly suggest that caution must be exercised however, when making management decisions based upon quantification of amyloid from a histological specimen.

References

1. Kristen AV, Brokbals E, Aus dem Siepen F et al. Cardiac Amyloid Load: A Prognostic and Predictive Biomarker in Patients With Light-Chain Amyloidosis. Journal of the American College of Cardiology 2016;68:13-24.
2. Fontana M, Pica S, Reant P et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015;132:1570-9.