CAP Evidence Based Guideline for Laboratory Evaluation of Amyloidosis: Role of Ultrastructural Evaluation: A Call to Action

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Abstract

Background: The College of American Pathologists (CAP) recently established a working group to create evidence-based standards for the laboratory evaluation of specimens for the presence and typing of amyloid fibrils (1). The purpose of this presentation is to review the guidelines, particularly as applicable to ultrastructural analysis, and to emphasize the ongoing need for studies utilizing ultrastructure to promote our understanding of the pathogenesis and pathology of amyloidosis.

Methods: The panel developed recommendations using the National Academy of Medicine standards for developing reliable clinical practice guidelines. A systematic review of the literature (4944 studies) was performed and recommendations were created based on the available evidence.

Results: Four conditional and three good practice recommendations were established to promote more standardized laboratory evaluation of specimens for amyloidosis. Specific to ultrastructural analysis (EM), available evidence (in our reviewed literature) comparing Congo red staining to EM was limited to two studies (2,3). Luigetti studied hereditary amyloidosis cases with sural nerve biopsy and found EM- Congo red concordance in 10/11 cases. EM highlighted amyloid presence in a hereditary amyloid mutation that is known to be difficult to detect with Congo red (Phe64Leu). In endomyocardial biopsies, Yamamoto found EM-Congo red concordance in 17/18 cardiac amyloidosis cases with EM identifying amyloid fibrils in an AL amyloidosis biopsy that was Congo red negative.

In the guidelines, EM was recommended as a gold-standard to which laboratories might validate any amyloid staining technique.

Conclusions: Ultrastructural analysis is still considered a gold standard for the evaluation of specimens for the presence of amyloid fibrils, and a reliable method by which to compare other laboratory established amyloid staining techniques. Evidence-based guidance for the use of ultrastructural analysis in clinical specimens was limited by the lack of many comparative studies. The future role of ultrastructural analysis in the clinical care of patients with amyloidosis will depend on ongoing research into amyloid pathogenesis and tissue injury and response to newer therapies.

References

1. Arch Pathol Lab Med. 2026;150:179–193; doi: 10.5858/ arpa.2025-0275-CP

2. Luigetti M, Romozzi M, Bisogni G et al. hATTR pathology: Nerve biopsy results from Italian referral centers. Brain Sciences. 2020;10(11):1-12. doi:10.3390/brainsci10110780.

3. Yamamoto M, Sato K, Murakoshi N et al. Additional diagnostic value of electron microscopic examination in endomyocardial biopsy in patients with suspected non-ischemic cardiomyopathy. J Cardiol. 2023;81(2):236-243. doi:10.1016/j.jjcc.2022.09.012.