The presence of anti-nuclear antibodies (ANA) is a hallmark of systemic autoimmune rheumatic diseases (SARD). The indirect immunofluorescence (IIF) assay on HEp-2 cells is commonly used routine test for the detection of ANA and was recently recommended as the screening test of choice by a task force of the American College of Rheumatology. However, approximately 20% of sera from apparently healthy individuals (HI) have been reported to test ANA positive, the majority of which are reported to be directed to the dense fine speckles 70 (DFS70) antigen. Even more important, the DFS IIF pattern has been reported in 33% of ANA positive HI, but not in ANA positive SARD sera. Since the intended use of the ANA HEp-2 test is to aid in the diagnosis of SARD, the reporting of anti-DFS70 antibodies and their associated pattern (DFS) as a positive test result, significantly reduces the specificity and the positive likelihood of the test. This has significant implications for ANA test algorithms. We summarize the current knowledge of anti-DFS70 antibodies and their impact on ANA testing. Base on recent data we present a test algorithm which considers the DFS pattern, the presence of anti-DFS70 antibodies and ANA. In addition, we present a novel method based on immunoadsorption of anti-DFS70 antibodies, which increases the specificity of the ANA HEp-2 test for SARD and has the potential to overcome a significant limitation of the ANA HEp-2 test.