Siemens Healthineers N Latex FLC Assays:

Compliance with International Guideline Recommendations

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Serum free light chain (sFLC) measurements are an increasingly important complementary test in the management of patients with monoclonal gammopathies, including prognostic stratification and monitoring of therapy responses.

Because of the history of sFLC testing, the use of FREELITE assays on the Siemens Healthineers nephelometric BN™ II System is widely considered as the reference method. This specific assay/system combination is therefore highlighted in many publications, guidelines, and assay IFUs. However, new methods have been introduced and continue to be released. Since no standardization is available for these tests, numeric values obtained from patient samples using these different commercial assays are not identical. This is also the case when identical assays are used on different analyzers.

For Siemens Healthineers N Latex FLC assays, clinical concordance with the FREELITE assays has been shown in many studies, enabling clinicians to be confident in using the Siemens Healthineers assays when switching from alternative methods.

But what about the guideline recommendations?

The clinical value of sFLC testing has been proven in numerous studies. Consequently, national and international guidelines have added sFLC testing to their recommendations. However, it still is occasionally claimed that FREELITE assays are the "gold standard" for FLC measurement and the only FLC assay recommended by guidelines.[1]

ESMO and IMWG guideline recommendations

The European ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up[2] of multiple myeloma recommend sFLC measurement, without referencing any method or technology. Any clinically approved method can therefore be used in accordance with these guidelines. ESMO guidelines also recommend that nephelometric technology—as used by the Atellica® NEPH 630* and BN Systems—be employed for the quantification of IgG, IgA, and IgM immunoglobulins, which are used together with sFLC and further parameters for diagnosing multiple myeloma.

The IMWG guidelines (2009 issue[3] and 2014 update[4]) state that the FLC assay is an "automated nephelometric assay", also highlighting the importance of this sensitive, reliable technology for the quantification of free light chains. Regarding the assay used, FREELITE was the only commercially available FLC assay in 2009 and was therefore specifically named in combination with the BN II nephelometer.

The 2014 update to the IMWG guidelines no longer highlights a specific assay, except in a footnote regarding the use of the 1:100 ratio of uninvolved vs. involved free light chains in multiple myeloma or smoldering myeloma. Equivalence of the N Latex FLC assays to the FREELITE assays has also been shown using the 1:100 ratio.[5]

Therefore, international guidelines clearly support the ability of laboratories to reliably and confidently change their sFLC testing method, keeping in mind that sFLC values obtained from different assays or even platforms cannot be used interchangeably. These guidelines also clearly prefer nephelometric determination. When switching methods, clinical concordance data between methods and establishment of a new baseline for patients facilitate a smooth conversion.

*Not available for sale in the U.S.

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It is important to remember that the difference in numeric values is observed not only when changing the assay, but also when changing the analyzer model. This has been described in many publications[6] and can be verified in EQA schemes such as the UK NEQAS sFLC scheme, in which every assay/system combination has a separate peer group. These variations have also been recognized by the U. S. Food and Drug Administration (FDA) when approving sFLC assays for use in the United States: "Free light chain results for a given specimen determined with assays from different manufacturers or on different systems can vary due to differences in assay methods and reagent specificity. ... Values obtained with different assays or systems cannot be used interchangeably. ...**Prior to changing assay or system, the laboratory MUST confirm baseline values for patients being serially monitored."**[7]

Therefore, for compliance with national or international recommendations, clinical concordance of the different methods and baselining are key when switching to another assay or analyzer.

N Latex FLC assays on Siemens Healthineers Atellica NEPH 630* and BN II Systems comply with IMWG guideline recommendations, as shown below:

Table 1. Compliance with IMWG guideline recommendations for N Latex FLC assays on nephelometric Atellica NEPH 630* and BN II Systems.

	IMWG Guideline Recommendations[3,4]			
	Diagnosis and monitoring of multiple myeloma**	**Assessment of smoldering myeloma****	**Clinical concordance with FREELITE assays**	**Nephelometry**
N Latex FLC assays on Siemens Healthineers platforms	✓	✓	✓	✓

**Not available for sale in the U.S.*
***Siemens Healthineers FLC assays are intended to be utilized as an aid in the diagnosis of multiple myeloma.*

References:
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3. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009;23(2):215-24.
4. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548.
5. Henriot B, Rouger E, Rousseau C, et al. Prognostic value of involved/uninvolved free light chain ratio determined by Freelite and N Latex FLC assays for identification of high-risk smoldering myeloma patients. Clin Chem Lab Med. 2019;57(9):1397-1405.
6. Cotten SW, Shajani-Yi Z, Cervinski MA, Voorhees T, Tuchman SA, Korpi-Steiner N. Reference intervals and diagnostic ranges for serum free κ and free λ immunoglobulin light chains vary by instrument platform: implications for classification of patient results in a multi-center study. Clin Biochem. 2018;58:100-7.
7. 510(k) Substantial Equivalence Determination Decision Memorandum, 510(k) Number K150658 for The Binding Site Group, Ltd.

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