Interpretation of FREELITE assay results and the risk of patient misclassification

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Introduction

Since its introduction in 2002, free light chains (FLC) testing has become a key laboratory parameter for diagnosis and management of monoclonal gammopathies.[1] Most recommendations on diagnosis and management of monoclonal gammopathies published by the International Myeloma Working Group (IMWG) and other international societies refer to serum free light chains (sFLC)—mostly the ratio between involved and uninvolved FLC—as an indicator and differentiator of the different stages of monoclonal gammopathies.[2-6]

Currently, several assays for determination of sFLC are commercially available, of which some designs use polyclonal antibodies, whereas others use monoclonal antibodies.[7] In addition, there are two detection methodologies—nephelometric and turbidimetric—that can be used with different sFLC assays.

These two methodologies apply different detection and quantification principles to measure changes in cloudiness or turbidity in a sample resulting from aggregation of the antibody and antigen. Nephelometry measures the amount of light scattering caused by the particles in the solution, which increases in accordance with the level of cloudiness, while turbidimetry determines the light transmittance blocked by the particles in the solution, which decreases with increasing cloudiness. Nephelometry is known to have a sensitivity advantage over turbidimetry, allowing lower limits of quantitation (LoQ) compared to turbidimetry (Figure 1).

The FREELITE assay, a polyclonal assay from The Binding Site, can be used on either nephelometric systems (e.g., BN™ II System from Siemens Healthineers or Beckman Coulter IMMAGE 800 system) or turbidimetric systems (The Binding Site SPA PLUS and OPTILITE systems, Roche COBAS c and COBAS Integra systems, Hitachi 911/912/917/Modular P systems, ADVIA® Chemistry Systems from Siemens Healthineers). The first recommendation on free light chains testing in multiple myeloma patients was published in 2009 and refers to the nephelometric BN II System from Siemens Healthineers and the FREELITE kappa and lambda assays,[7] which were the only commercially available free light chain assays at the time, to establish the recommended diagnostic cutoffs.[8] However, all subsequent updates to this guideline[2] and other guidelines involving free light chains testing in multiple myeloma patients[3-6] refrain from mentioning or recommending specific assays or systems. Nonetheless, the updated criteria for the diagnosis of multiple myeloma published in 2014[2] and the ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up[3] clearly recommend automated nephelometry as the technology of choice to measure serum free light chains. However, the current lack of an international standard material makes it impossible to define a "true" sFLC value for a sample (kappa, lambda, or ratio). Thus, results of any FLC assay need to be interpreted in the context of clinical presentation and other laboratory indicators of the patient.

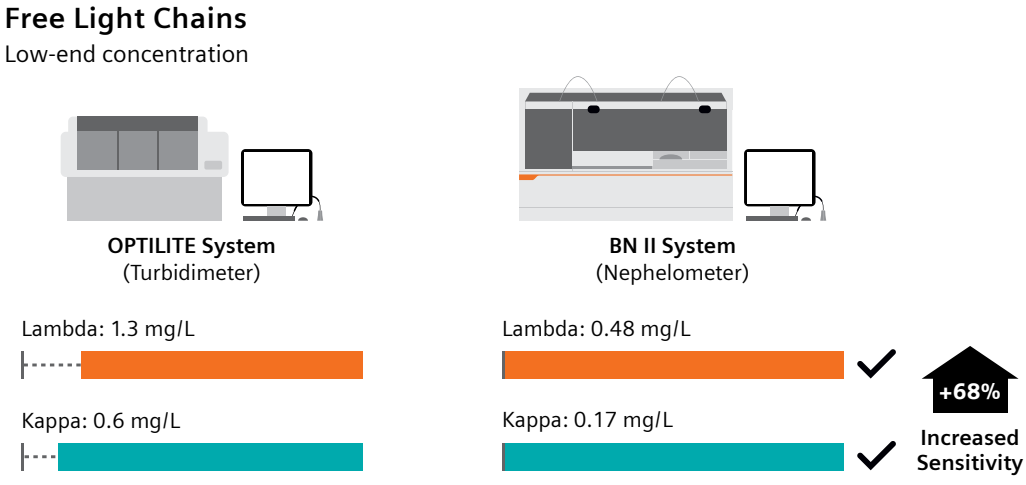

Figure 1. Limit of quantitation of the FREELITE assays on a turbidimeter (OPTILITE system from The Binding Site) and N Latex FLC assays on a nephelometer (BN II System from Siemens Healthineers). Source: Manufacturers' IFU.

Polyclonal vs. monoclonal antibodies: Does it make a difference?

Several free light chain assays have been introduced to the market.[7] Some make use of polyclonal antibodies, whereas others use monoclonal antibodies to determine free light chains in serum, urine, or cerebrospinal fluid (CSF) sample types. It is important to point out that the use of polyclonal or monoclonal antibodies for detection of FLCs may have an impact on assay results. Caponi et al., 2018,[9] showed that the polymerization status of the free light chains determines the extent to which free light chains are detected by the different assays. Polyclonal FREELITE assays and monoclonal N Latex FLC assays detect FLC kappa monomers and dimers with differing sensitivities. FREELITE assays detect mostly FLC lambda dimers, while N Latex FLC assays detect mostly FLC lambda monomers. The significance of these differences can be observed in comparison studies between the assays, which conclude that assays cannot be used interchangeably, as they yield different results.[10-15] These differences may also explain other clinically significant variations in performance between the polyclonal FREELITE assays and the monoclonal N Latex FLC assays. Nevertheless, the reference ranges are very comparable.

Numeric results, especially in pathologic samples, may be different, but clinical concordance is imperative for accurate result interpretation and monitoring. With the FREELITE assays being the first method to have been clinically validated, most of the recently launched sFLC assays have since proven concordance with and can therefore substitute for the FREELITE assays following "baselining" when switching to the new method.[16] It is also important to note that baselining is also required when changing the analyzer type—even when continuing to use the same assay.

Influence of the analyzer on FLC assay results

While differences between FLC assays, specifically the non-interchangeability of FREELITE and N Latex FLC assays, have been reported in numerous publications, the influence of the system and detection method (nephelometry or turbidimetry) used to run an assay and its impact on clinical decision making have been largely underrated. Additionally, the polyclonal assay principle of FREELITE assays might also contribute to the large variability observed.[17]

The FREELITE assay reference intervals, originally established on a nephelometric BN II System in 2002,[9] have been adopted for other platforms as well, as outlined in the manufacturer's instructions for use.

However, comparison studies of the FREELITE assays on different systems show significant differences among the systems. Comparing FREELITE assays on BN II System (nephelometer) vs. an OPTILITE system (turbidimeter), a bias of +10.9% for FREELITE kappa assay and +17.7% for FREELITE lambda assay was reported between the two systems.[18] These results are of particular interest considering that clinical decision-making points such as the upper limit of the reference interval or the "rule 100" for risk stratification of multiple myeloma[2] were established using FREELITE assays on BN II System. Currently, the FREELITE assays are most often measured with the OPTILITE turbidimeter. Taking system biases into account, patients with results close to clinical decision points may be misclassified if FREELITE assays are used in combination with the OPTILITE system.

Comparison of FREELITE assays on an undefined system from The Binding Site (turbidimeter) and FREELITE assays on a Beckman Coulter IMMAGE 800 system (nephelometer) also yielded a bias of –21.4% for FLC kappa (KFLC), –10.9% for lambda free light chains FLC lambda (LFLC), and –10.5% for the FLC ratio and Passing-Bablok slopes of 0.802 for KFLC, 0.888 for LFLC, and 0.781 for FLC ratio.[19] Why the authors of this study consider these results to indicate a "very good concordance" is difficult to comprehend, especially when considering the identical reference interval mentioned in the respective package inserts.

The different performance of the FREELITE assays on various analyzers can also be easily tracked in external quality assessment (EQA) rounds where each system/assay combination has a separate peer group to overcome the numeric discrepancies in single samples. Another source is the FDA 510(k) memorandum for FREELITE assays on the OPTILITE system stating: "Prior to changing assay or system, the laboratory MUST confirm baseline values for patients being serially monitored." (https://www.accessdata.fda.gov/cdrh_docs/reviews/k150658.pdf)

N Latex FLC assays have been applied on BN II System, BN ProSpec® System, and their successor Atellica® NEPH 630 System (all Siemens Healthineers nephelometers) as well as Atellica CH 930 Analyzer, a turbidimetric analyzer. In contrast to FREELITE assay results on various analyzers as described above, comparability of N Latex FLC assay results among these systems from Siemens Healthineers was shown to be very consistent in internal method comparison studies (Passing-Bablok regression slope ranging from 0.914 to 1.01, intercept ranging from –0.07 to +0.12 mg/L, and Pearson correlation coefficients [r] of 0.970 to 0.999 in comparisons of BN II System to BN ProSpec System and BN ProSpec System to Atellica CH 930 Analyzer). To prevent discordant results, N Latex FLC assays must not be applied to third-party analyzers.

The effect of assay and system combinations on treatment and clinical decision making

A recent evaluation of 27 external quality assessment (EQA) rounds distributed from 2015–2020 to 11–16 hospital laboratories in Sweden reported results for different assay/platform combinations (FREELITE assays/Beckman system, FREELITE assays/Roche system, FREELITE assays/Siemens Healthineers systems, and N Latex FLC assays/Siemens Healthineers systems). This evaluation revealed that the combinations of reagents and instrument platforms used for KFLC showed an acceptable correlation ranging from 0.81 to 1.2, but that for LFLC, no clear concordance among the various assay/platform combinations could be observed.[20] These results demonstrate clear combination-specific differences for FLC measurements, which are currently not considered when using the established clinical decision points for FLC using FREELITE assays. The authors of the analysis concluded that medical practitioners should be made aware of the implications, specifically that the choice of reagent/system combinations may have an impact on patient treatment and clinical decisions. In a study comparing N Latex FLC and FREELITE assays on a nephelometer as well as FREELITE assays on a turbidimeter (Roche COBAS 6000 system), the authors also concluded that "monitoring of disease response requires FLC analysis on the same platform using the same reagents," as considerable disagreement in patient classification was observed based on the assay/system combination used.[17]

Utility of FREELITE assay reference intervals

The magnitude by which reference intervals for KFLC, LFLC, and FLC K/L ratio are affected by the assay and system used in case of the FREELITE assays was well-illustrated in a study published by Cotton et al. in 2018.[16] The authors stressed the marked differences in distribution for all three FLC parameters, as shown in Figure 2, and highlighted the potential impact on the resulting patient classification.

The four platforms investigated—The Binding Site SPAPLUS, The Binding Site OPTILITE, Roche COBAS 6000 c601, and Beckman Coulter IMMAGE 800 systems—did not yield an acceptable transference of the KFLC reference interval as reported by the manufacturer of the FREELITE assay, which resulted in up to 23% of patients being misclassified (on the Roche COBAS 6000 system). As LFLC was not so much affected by the platform, the FLC ratio exhibited a misclassification rate of up to 8.7% (on the OPTILITE system). Interestingly, only the nephelometer (Beckman Coulter IMMAGE 800 system) ideally demonstrated the reference intervals of the FREELITE assays and yielded no misclassification.

A recent letter to the editor also discussed the wide variability of FREELITE assay reference intervals for FLC ratio depending on the system used and the risk for misclassification (Figure 3).[21]

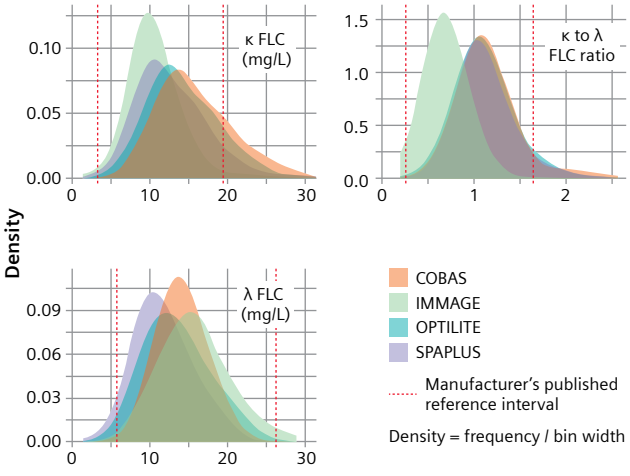

Figure 2. Distribution of KFLC, LFLC, and FLC ratio results in reference sera. Serum KFLC, LFLC, and FLC ratio results (n = 126) in reference sera were determined by the COBAS, IMMAGE, OPTILITE, and SPAPLUS systems and plotted as a function of the density of results (density = frequency/bin width). Representative results determined from one of two OPTILITE instruments are shown. The vertical dashed lines indicate the manufacturer's reported lower and upper FLC reference limits. Adapted from Cotten et al, 2018.[16]

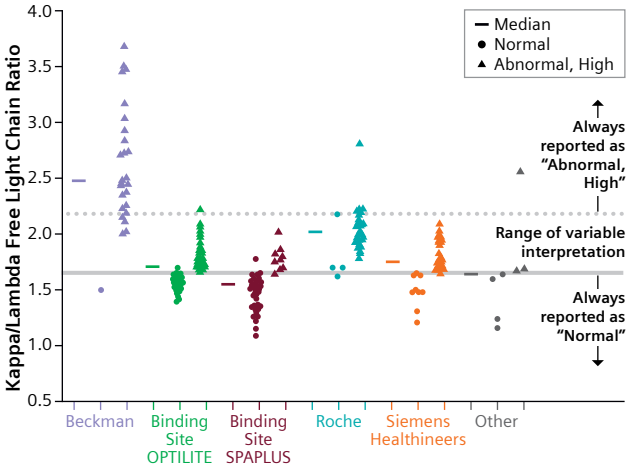

Figure 3. Distribution of serum FLC kappa/lambda ratios (FLCr) reported by proficiency testing participants on different platforms. Nonconsensus for FLCr was partially due to the wide distribution of values reported for this specimen, which ranged from 1.09 to 3.70 Adapted from Fink et al., 2023.[21]

Astonishingly, almost all assay/system combinations in this study have reference intervals with a median above the manufacturer's uniform reference interval's upper limit of normal (1.65), meaning that more than 50% of results might be falsely positive. The median values also illustrate the marked differences between the reference intervals shown and the lack of consensus among them. Consequently, the authors state "that revised clinical guidelines should avoid citing assay or instrument-specific FLCr RI, and that laboratories may consider establishing the FLCr RI using local patient populations in collaboration with clinical teams."[21]

The observation that reference intervals for the FREELITE assays are more than 20 years old, and thus may no longer be clinically accurate, was reported as early as 2016, when an abnormal FLC κ/λ ratio was observed in 36.4% of patients without evidence of monoclonal gammopathy.[22]

The importance of reference range intervals in patient classification

A more recent investigation of KFLC, LFLC, and FLC ratio reference intervals for FREELITE assays on the OPTILITE system concluded that "these ranges are different from those provided by the manufacturer and from those used in most studies in the literature, which may lead to patient misclassification."[23]

Furthermore, two recent studies observed a shift toward a higher FLC K/L ratio in FREELITE assays (Figure 4), raising additional concern about patient misclassification when using the FREELITE assay reference interval from 2002 as indicated by the manufacturer.[24,25]

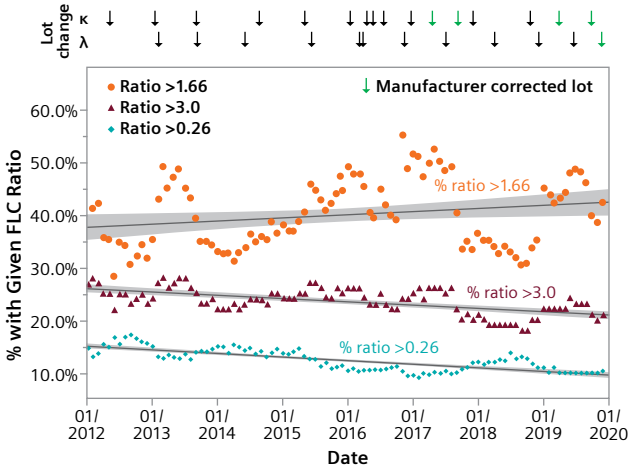

Figure 4. Free light chain ratio reporting frequency over time demonstrates an increasing trend in elevated abnormal ratios primarily in the >1.66 to 3 range from 1/2012 to 1/2020. The upper X axis demonstrates lot changes, including those corrected by the manufacturer (green arrow). The line of fit is shown with its 95% confidence interval, showing significant trends up or down ($P < 0.0001$). Frequency of low abnormal ratios (<0.26) and ratios above the renal reference range (>3.0) both demonstrate a downward trend, while the percentage above the normal reference range (>1.66) demonstrates an increasing trend. Adapted from Murray et al., 2020.[25]

Consequently, Minnema et al.[26] noted in their comment on the new renal reference intervals from the iStopMM study[27] that the manufacturer of the FREELITE assays should "perform a platform-wide recalibration bringing the FLC ratio reference ranges back to 2002" or "introduce novel FREELITE reference intervals, not only for patients with impaired renal function but also for healthy controls."

Schroeder et al.,[28] in their recent retrospective analysis of FREELITE reference intervals showing a significant discrepancy between the claimed and real reference intervals, came to a similar conclusion: "These findings corroborate recent reference interval studies and support recommendations for independent re-evaluation of intervals by institutions as well as an update of international guidelines."

All this evidence clearly indicates that using the current manufacturer's reference interval for the FREELITE assay as well as the IMWG definition for multiple myeloma[2] on platforms other than BN II System might lead to patient misclassification and possible mistreatment.

Influence of kidney function on FLC results

Renal impairment is common in patients with monoclonal gammopathies. As free light chains are primarily cleared via the kidneys, decreased renal function results in an increasing enrichment of free light chains in the blood and thus greatly affects sFLC measurements.

Impaired kidney function influences the serum free light chains results of the polyclonal FREELITE assays, particularly in FLC lambda, necessitating use of at least two different reference intervals for FLC ratio, depending on the renal status of the patient[15,28,29] or complex mathematical processes such as principal component analysis.[30]

Even more striking is that the analysis of FREELITE assay sFLC results derived from the 6561 patients included in the large iStopMM study who were not under renal replacement therapy showed no evidence of monoclonality and had an eGFR <60 mL/min. The evaluation resulted in a proposal of new renal reference intervals for FLC ratios for FREELITE assays that are dependent on the patient's kidney status, which were 0.46–2.62, 0.48–3.38, and 0.54–3.30 for eGFR 45–59, 30–44, and <30 mL/min/1.73 m^2 groups, respectively.[29]

The authors conclude that current reference intervals for FLC and FLC ratio (of the FREELITE assay) are inaccurate in CKD patients and propose new eGFR-based reference intervals be implemented. However, these new intervals have not yet been implemented.

The manufacturer of the FREELITE assays currently only recommends using a separate reference interval based on a study from 2008[31] if the estimated glomerular filtration rate is below 60 mL/min/1.73 m² (0.37–3.1 instead of 0.26–1.65). It can be questioned if all laboratories are aware of these different reference ranges and if they have correctly calculated the patient's kidney function data to the adjusted reference range. In any case, each patient's kidney status must be known to apply the manufacturer-recommended reference range, and the cutoffs for the risk stratification ("rule 100" or >100 mg/L of involved light chain) should be challenged, even if not taking the iStopMM study results into account.

In contrast, reference intervals for the monoclonal N Latex FLC assay ratio are stable and can be used irrespective of renal function status.[31-33] Xu et al. in 2022[34] showed the close linear relationship of sFLC results obtained with N Latex FLC assays and renal impairment in comparison to the "poor" correlation observed with the FREELITE assays (Figure 5).

The authors of the study concluded: "The ratio of FLC K/L determined by the N-Latex method is not affected by renal function and remained stable within the recommended range."[34]

Thus, even if the renal status of a patient is unknown, N Latex FLC assays can be used to detect the presence of a monoclonal gammopathy with confidence.

If I use the FREELITE assays, am I following the IMWG recommendations?

The simple answer: It depends.

Differences in FREELITE assay results depend on the measuring system. In addition, minor yet significant drift of assay performance not only impacts the reference interval, but also the classification rules for multiple myeloma ("rule 100"[2]). To re-emphasize the point: These rules were established using the FREELITE assays on BN II System more than two decades ago using a diagnostic range[28] and have not been updated. Current evidence strongly suggests the "rule 100," which was valid for the FREELITE assays on BN II System, may not be valid for the FREELITE assays on the OPTILITE analyzer or other turbidimetric systems.

Despite the lack of clinical revalidation of important clinical decision points, many users still consider using the FREELITE assays as working in accordance with the IMWG recommendations from 2009[7] and 2014.[2] Based on the scientific evidence outlined here, this assumption cannot be supported.

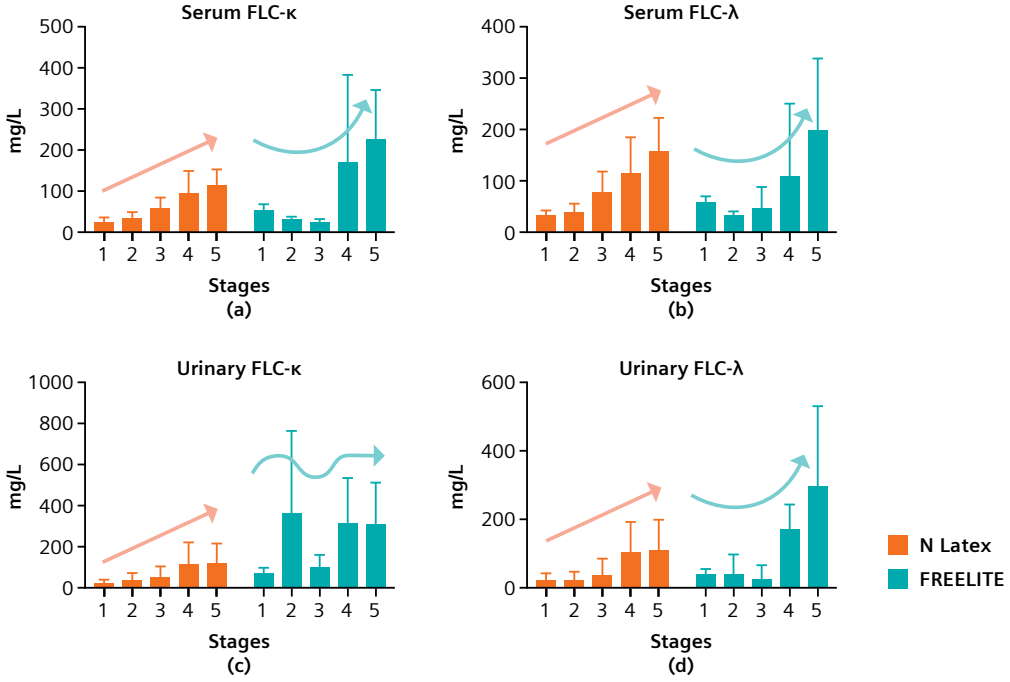

Figure 5. Expression of serum and urinary FLC detected by two methods in different renal functions: (a) serum KFLC; (b) serum LFLC; (c) urinary KFLC; (d) urinary LFLC. FLC: free light chain. Kidney staging according to KDIGO guidelines. Adapted from Xu et al., 2022.[34]

Summary

History: FREELITE assay reference intervals were established on BN II System in 2002 and adopted identically for all platforms used to run the assays.

More history: Clinical cutoffs (i.e., "rule 100") for sFLC in the IMWG guidelines' updated criteria for the diagnosis of multiple myeloma[2] were also established with the FREELITE assays on BN II System.

Reality: FREELITE assay reference intervals differ significantly from the original reference intervals and also between each other. Most importantly, the manufacturer's reference intervals do not match for the OPTILITE system, and for patients with renal impairment.

More reality: Considering the significant differences in FREELITE assay results on various systems, the IMWG 2014 clinical cutoffs should only be valid for FREELITE assays run on BN II System.

Clinical concordance: Although results are not interchangeable, clinical concordance to the FREELITE assays has been shown for most commercially available assays, so they can be used with confidence.

FDA recommendation: FDA requests baselining when switching the system or sFLC assays.

Choose N Latex FLC assays:

- One reference interval across patient populations and systems independent of renal impairment
- Stable results (negligible lot-to-lot variation) due to monoclonal assay principle using nephelometry
- Most complete clinical claims for sFLC testing, including "evaluation and monitoring of MGUS" cleared for N Latex FLC assays under IVDR in July 2023, which was not the case for other assays at that time

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