International Myeloma Working Group (IMWG) Guidelines for Serum Free Light Chain Analysis in Multiple Myeloma and Related Disorders

The following guidelines from the International Myeloma Working Group describe the potential uses of the serum free light chain （SFLC） assay and distinguish which uses have proved their utility and which are still undergoing investigation.

IMWG GUIDELINES FOR SERUM FREE LIGHT CHAIN ANALYSIS IN MULTIPLE MYELOMA AND RELATED DISORDERS[1]

For the more than 3% of myeloma patients who have non-secretory or oligosecretory disease, and for the majority of patients with AL amyloidosis (AL), the traditional methods of measuring circulating monoclonal immunoglobulins (electrophoresis, immunoelectrophoresis, immunofixation electrophoresis, and nephelometric measurement of immunoglobulin heavy chains of serum) are not adequate. The development of an assay that measures serum immunoglobulin-free light chains has demonstrated utility for monitoring these patients and for other specific indications, such as monitoring heavily-pretreated patients at relapse.

The following guidelines from the International Myeloma Working Group describe the potential uses of the serum free light chain （SFLC） assay and distinguish which uses have proved their utility and which are still undergoing investigation.

SFLC assay for screening at diagnosis

- The combination of serum immunoelectrophoresis (IFE), serum protein electrophoresis (PEL), and serum free light chain （SFLC） assay are recommended for screening at diagnosis.
- For the purpose of screening for monoclonal proteins for all diagnoses except AL, the SFLC assay can replace the 24-hour urine IFE, BUT after diagnosis, the 24-hour urine for PEL and IFE should be done. For AL screening, the urine IFE should still be done in addition to the serum tests, including SFLC.

Prognostic value of the SFLC assay

- Baseline values of the serum SFLC ratio are prognostic for:
    - MGUS (monoclonal gammopathy of undetermined significance)
    - Smoldering myeloma
    - Symptomatic myeloma
    - Solitary plasmacytoma
    - AL amyloidosis

The FLC assay in response assessment

- Treatment-related immunosuppression of the uninvolved light chain (lambda for kappa patients, and vice versa) can make the assay unreliable for monitoring response in patients with secretory disease.

- Routine serial use of the SFLC assay is recommended for oligosecretory disease; hematologic response can therefore be best assessed with SFLC assay in:
    - AL amyloidosis
    - "Non-secretory" myeloma (not yet fully validated)
    - Light chain deposition disease (not yet fully validated)

Response Criteria for FLC

	Minimum deemed measurable	PR	CR	sCR	Progression
AL without measurable serum or urine M-protein	iFLC $\geq$ 100mg/l	50% reduction of iFLC	Normal rFLC and CR by IFE and bone marrow	ND	50% increase of iFLC to > 100 mg/l
AL with measurable serum or urine M-protein	ND	ND	ND	ND	ND
MM without measurable serum or urine M-protein	iFLC $\geq$ 100mg/l and rFLC abnormal	50% reduction of dFLC	ND	Normal rFLC & CR by IFE and bone marrow	50% increase of dFLC
MM with measurable disease	Use of FLC not recommended	Use of FLC not recommended	Use of FLC not recommended	Normal rFLC & CR by IFE and bone marrow	Use of FLC not recommended

Abbreviations: iFLC, inv- restricted disease; dFLC, difference between iFLC and uninvolved FLC; rFLC ,free light chain ratio; ND, not defined.
aMeasurable M protein includes serum M protein of at least 1 g per 100 ml or a urine M-protein of at least 200 mg/24 h for myeloma patients (100 mg/24 h for AL patients).

The FLC assay in the context of renal insufficiency

- Although renal failure increases the levels of both kappa and lambda light chains, it does not result in an abnormal ratio.
- Interpreting serial measurements of iFLC in patients with oligosecretory myeloma. LCDD, or amyloidosis who are on dialysis or who have markedly abnormal renal function is very challenging, and response assessment has not been validated. However, following the dFLC or iFLC while noting the uninvolved light chains can provide information.

Caveats with the free light chain (FLC) assay

- Clinical
    - The test must be interpreted in the context of a clinical situation. If a patient is in the midst of an infection or a flare-up of a rheumatologic condition, the test should be repeated at a later date.
- Technical
    - There can be lot-to-lot variation between batches of polyclonal FLC antisera, which can produce inconsistent results.
    - Some monoclonal light chains (particularly kappa) do not dilute in a linear fashion and may be underestimated.
    - Changes in the amino acid sequence of the light chain may render certain light chain epitopes unrecognizable to the FLC reagents.
    - Extreme polymerization can cause an overestimation of light chains by as much as 10-fold.
    - Very high levels of light chains can cause antigen excess, which in turn can result in falsely low SFLC results with nephelometric techniques.
    - For large multi-center clinical trials, using a centralized lab is an option to avoid lot-to-lot variation issues.

[1]A Dispenzieri *et al.* International Myeloma Working Group guidelines for serum free light chain analysis in multiple myeloma and related disorders. *Leukemia* (2008), 1-10.