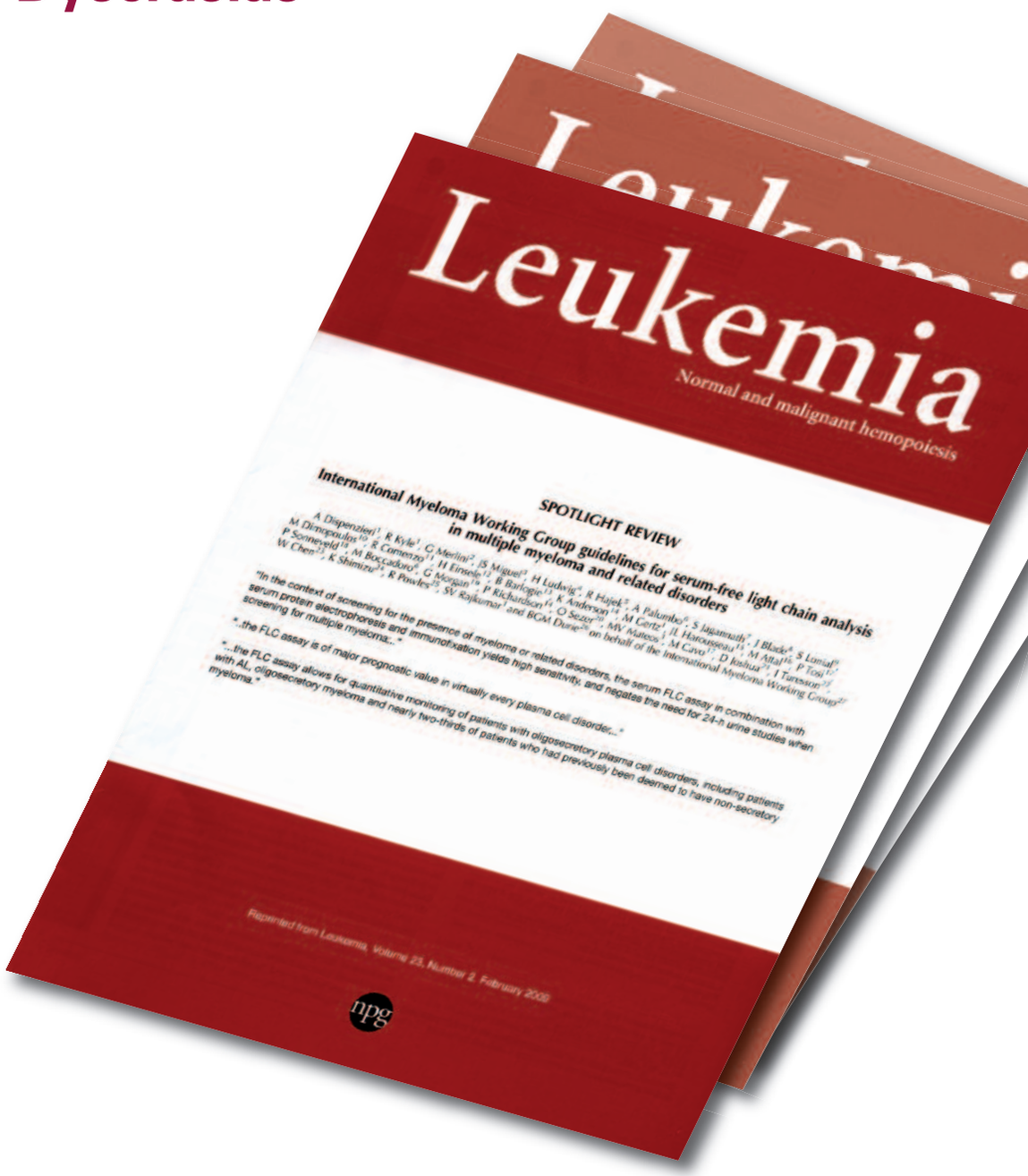
Freelite™

Serum Free Light Chain Assays

Recommended by
International Myeloma Working Group guidelines
for B cell Dyscrasias



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Freelite™
Serum Free Light Chain Assays

What is Freelite?

There is significant clinical evidence indicating the benefit of the use of serum free light chain (FLC) assays in initial screening for monoclonal gammopathies, identifying AL amyloidosis and Nonsecretory Multiple Myeloma (NSMM) patients which are missed by conventional electrophoretic methods, as a prognostic indicator for progression in myeloma, for risk stratification of Monoclonal Gammopathy of Undetermined Significance (MGUS) patients and rapid evaluation of treatment efficacy.[1]

Freelite is a sensitive, specific marker of kappa and lambda FLC in serum and provides quantitative measurement of:

- free kappa (κ) in serum
- free lambda (λ) in serum
- the serum free kappa/free lambda ratio (κ/λ)

The serum FLC ratio is a strong indicator of monoclonality and is valuable for distinguishing monoclonal from polyclonal diseases.

Freelite is comprised of two immunodiagnostic assays; one for kappa and one for lambda. Affinity purified polyclonal antibodies, reacting specifically with the free forms of kappa and lambda light chain, are precoated onto latex particles. These latex reagents are used to produce nephelometric and turbidimetric kits that are specific for FLC. The greater sensitivity of these assays means that serum FLC can now be detected and quantified through to the normal range in routine practice. Assays are available on a wide range of automated platforms, ensuring accuracy and reduced hands on time.

Conventional laboratory analysis for monoclonal gammopathies has involved serum protein electrophoresis (SPE) or capillary zone electrophoresis (CZE) plus urine protein electrophoresis (UPE) (for Light Chain Multiple Myeloma, Bence Jones Protein), followed by immunofixation electrophoresis (IFE). Now, with **Freelite**, a more sensitive and specific protocol can be implemented to significantly increase detection of B cell dyscrasias.

Freelite is available for use on a range of analysers including Binding Site's SPAPLUS™.

Freelite is Recommended for Use:

- In screening
- At diagnosis
- For prognosis
- When monitoring

In Patients With:

- Light Chain Multiple Myeloma (LCMM)
- Nonsecretory Multiple Myeloma (NSMM)
- Intact Immunoglobulin Multiple Myeloma (IIMM)
- Smouldering Multiple Myeloma (SMM)
- Solitary Plasmacytoma
- AL amyloidosis
- Monoclonal Gammopathy of Undetermined Significance (MGUS)

Freelite enables compliance to International Guidelines

The International Myeloma Working Group (IMWG) guidelines' [1] key recommendations for the use of **Freelite** are:

- The serum FLC assay in combination with SPE and sIFE is sufficient to screen for pathological monoclonal plasmaproliferative disorders other than AL amyloidosis which requires all the serum tests as well as a 24 h urine.
- The serum FLC assay should be measured at diagnosis for all patients with MGUS, smouldering or active MM, solitary plasmacytoma and AL amyloidosis.
- Serial FLC ascertainment should be routinely performed in patients with AL amyloidosis and MM patients with oligosecretory disease.
- Serum FLC should be measured in all patients who have achieved a complete response to determine whether they have obtained a stringent complete response.

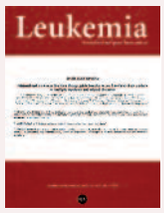
Are you following the IMWG Guidelines?

Freelite - Recommended for use at Diagnosis

Remove the inconvenience and ensure the best detection rate

Optimise your detection rate of B cell dyscrasias by including **Freelite** in your laboratory work up. The combination of **Freelite** and serum protein electrophoresis (SPE) enables sensitive quantification of serum free light chains (FLC) for diagnosis. This means urine studies and serum immunofixation electrophoresis (IFE) can be ordered more selectively.[2]

International Guidelines recommend the use of Freelite



The International Myeloma Working Group (IMWG) Guidelines[1] state that **Freelite** should be used for the diagnosis, monitoring and prognosis of B cell dyscrasias.
At diagnosis "The serum FLC assay in combination with serum PEL and serum IFE is sufficient to screen for pathological monoclonal plasmaproliferative disorders other than AL, which requires all the serum tests as well as the 24-h urine IFE."

Accuracy of different diagnostic approaches for monoclonal proteins

Using currently available data Table 1 shows the detection rate for all Multiple Myelomas (MM), AL amyloidosis, Light Chain Multiple Myelomas (LCMM) and Nonsecretory Multiple Myelomas (NSMM) using different combinations of diagnostic tests.[3,4,5,6,7,8]
It is important to note that for LCMM, **Freelite** detected 100% of patients whereas SPE and urine protein electrophoresis (UPE) together only detected 90%.
Optimal pick up rate for all paraproteins can be achieved by simply performing SPE or capillary zone electrophoresis (CZE) plus **Freelite** without the need for a urine sample.

Protocols	% of Paraproteins detected			
	*Myeloma	AL	LCMM	NSMM
SPE/CZE alone	90	50	40 - 57	0
SPE/CZE, serum IFE	95	70	75	0
SPE/CZE and UPE	95	75	90	0
SPE/CZE, UPE, serum and urine IFE	97	90	95	0
Freelite alone	96	98	100	68**
SPE/CZE and **Freelite**	99	98	100	68**
SPE/CZE **Freelite** and serum IFE	99	98	100	68**

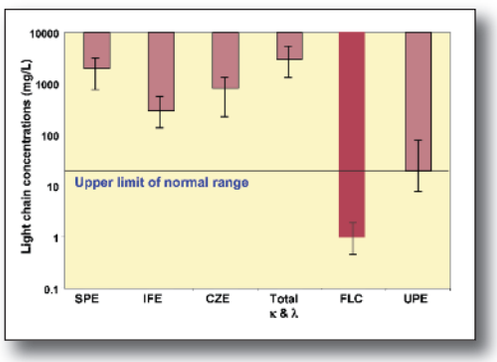
Table 1. Accuracy of different diagnostic approaches for monoclonal proteins

*Myeloma is inclusive of samples from patients identified with Intact Immunoglobulin Multiple Myeloma, Light Chain Multiple Myeloma and Nonsecretory Multiple Myeloma.
**A further 4/28 patients with suppression of one or both free light chains were identified in addition to this 68% equaling 82%.[4]

A combination of SPE/CZE and Freelite gives the optimum detection rate.

Improve your accuracy in detecting B cell dyscrasia whilst shortening the diagnostic pathway

The superior sensitivity of **Freelite** allows measurement down through the normal range. This enables more accurate detection of MM, LCMM, AL amyloidosis and other B cell dyscrasias.[9]



Listen to the experts

"...the use of serum PEL plus FLC provides a simple and efficient initial diagnostic screen for the high-tumor-burden monoclonal gammopathies such as MM, WM and SMM. Urine studies and serum IFE can be ordered more selectively." [2]

"...most laboratories find it difficult to obtain both serum and urine samples from patients. In this hospital, despite publicity from the laboratory, concurrent urine samples are received from <40% of patients." [10]

"...performing urine studies can become much more selective. This approach will not only reduce cost but also spare patients the inconvenience of a 24-hour urine collection" [11]

"Urine tests are no longer necessary as part of the screening algorithm for identifying monoclonal gammopathies..." [11]

"Additional diagnostic information is gained by adding serum FLCs to SPEP as first-line tests for investigating possible B-cell disorders. The quality of the diagnostic service is enhanced by more confident exclusion of light chain disorders and improved interpretive assessment of SPEP and immunofixation electrophoresis". [10]

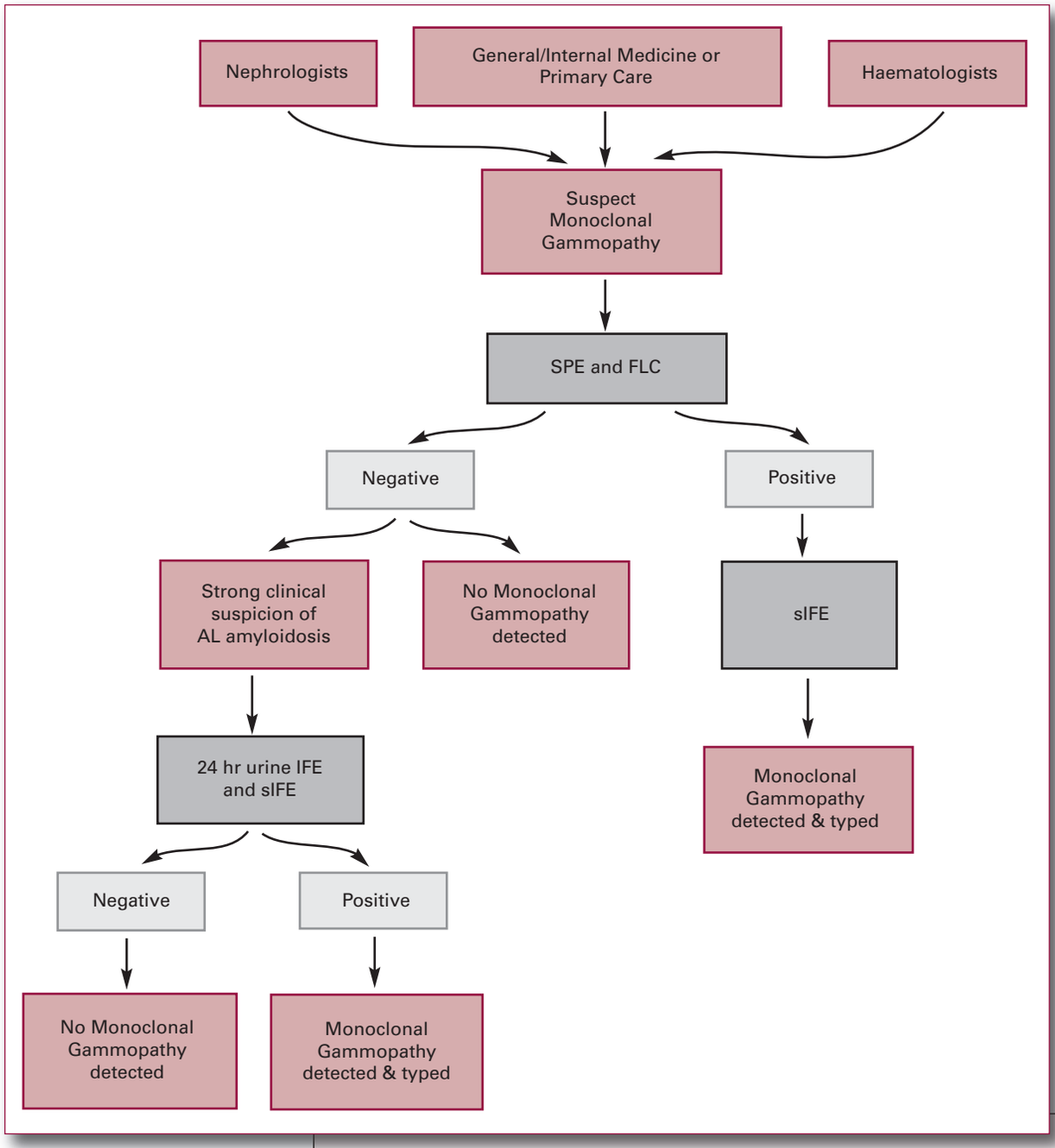
"...we have now adopted SPEP and serum FLCs as our first-line tests for the investigation of possible B-cell disorders. Because no substantial pathology would have been missed by replacing urine Bence Jones Protein with serum FLCs, we no longer require a urine sample as part of the initial screen." [10]

"Critically, due to the poor compliance of urine sample provision, serum FLC analysis provided the most effective practical means of determining monoclonal FLC production in a diagnostic setting." [12]

At diagnosis, urine tests are no longer necessary.

Suggested laboratory diagnosis algorithm

An algorithm combining SPE and **Freelite** is shown below.



An algorithm combining SPE and Freelite will allow for the most sensitive and specific identification of all significant monoclonal proteins and negate the requirement for urine samples for screening for Bence Jones Protein.

Peace of mind

Adding **Freelite** to your initial testing algorithm improves:

- Patient compliance
- Performance
- Efficiency

Patient compliance

Reports of patient compliance in producing 24 hour urines of only 40% have been cited.[10] Traditional protocols where urine is requested heavily impact on both clinical and lab resources with no added benefit.[12] Additionally lack of compliance can be due to many factors including renal impairment, embarrassment, inconvenience and the fraility of patients. Now you can avoid these problems and obtain a sample every time as only a blood sample needs to be collected. Conveniently, you can collect the blood at the same time as blood is taken for other diagnostic tests.

Performance

Freelite provides rapid, early, quantitative and precise results from a simple serum sample improving turnaround times for myeloma patient results.
Freelite offers sensitivity gains over urine electrophoresis and avoids misleading urine results due to impaired renal function.[13]
In addition the FLC ratio when combined with just SPE offers increased detection of monoclonal proteins compared with immunofixation of both serum and urine.[14]

Efficiency gains

In the clinic:	In the laboratory:
Just a simple blood collection	No need to chase for urine samples
No need to chase for urine samples	No requirement for storage of large volume samples
Improve the turnaround time for a patient result [10]	No time consuming concentration of urines
Reduce testing costs [11]	Maximise workflow through automation
Use the same reliable test in screening that you use in monitoring	Reduce hands on time and release valuable labour resource
Fully quantitative assay	Assay time of less than 20 minutes
No significant pathology missed by replacing urine Bence Jones Protein[10]	Improve the turnaround time for a patient result [10]
	Reduce testing costs [11]
	Use the same reliable test in your initial evaluation that you use in monitoring

Make the change and reap the rewards.

Freelite – Recommended for Prognosis

Freelite can help you identify patients with a high risk of progression and poor prognosis as it is an independent prognostic indicator in Multiple Myeloma (MM) patients

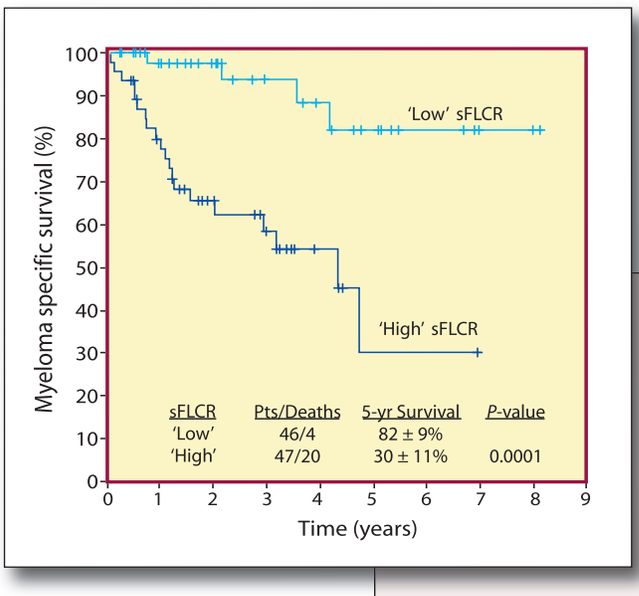
The International Myeloma Working Group (IMWG) guidelines[1] recognise **Freelite** as an important prognostic tool, for Monoclonal Gammopathy of Undetermined Significance (MGUS), smouldering and active MM, solitary plasmacytoma and AL amyloidosis. In conjunction to this, several publications relating to over 1600 patients have highlighted **Freelite** as an independent marker of prognosis in plasma cell dyscrasias.

Listen to the experts

"High baseline SFLC levels were a reflection of higher tumor burden, higher degree of disease aggressiveness and light-chain-only MM with its greater propensity for renal failure." [15]

"The serum FLC ratio at initial diagnosis is an important predictor of prognosis in myeloma."[16]

"In conclusion, baseline sFLCR appears to be an easily determined powerful, independent and very promising novel prognostic factor for survival in patients with newly diagnosed MM." [17]

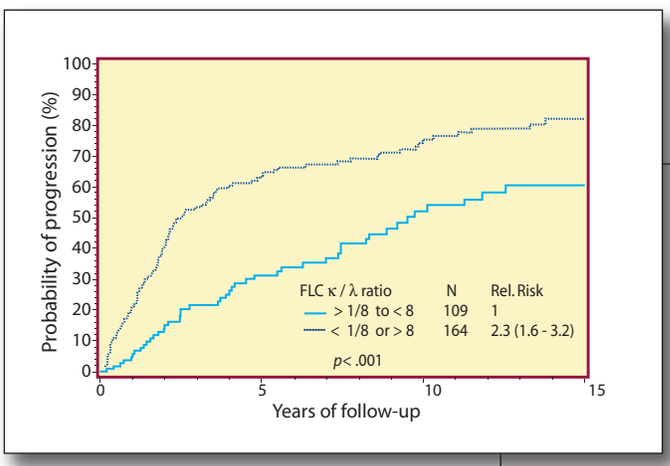


"The 5-year disease-specific survival was 82% and 30% in patients with sFLCR lower than and equal or greater than the median, respectively (P=0.0001). sFLCR was an independent prognostic factor." [18]

sFLCR = serum free light chain ratio

Determine likely progression of Smouldering Multiple Myeloma patients

Smouldering Multiple Myeloma (SMM) is an asymptomatic plasma cell disorder associated with a high risk of progression to symptomatic MM. In a recent study, 273 patients with SMM had baseline serum free light chain (FLC) concentrations measured. The authors concluded: **"The serum immunoglobulin FLC ratio is an important additional determinant of clinical outcome in patients with SMM."** [19]



Risk of progression to myeloma or related disorder in 273 patients with SMM.
Risk of progression of SMM to active myeloma using serum κ to λ FLC ratio of less than 0.125 (<1:8) or more than 8 (top curve) versus 0.125 to 8 (bottom curve)

This research was originally published in *Blood*. Dispenzieri *et al*. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111:2:785-789. © *American Society of Hematology.* [19]

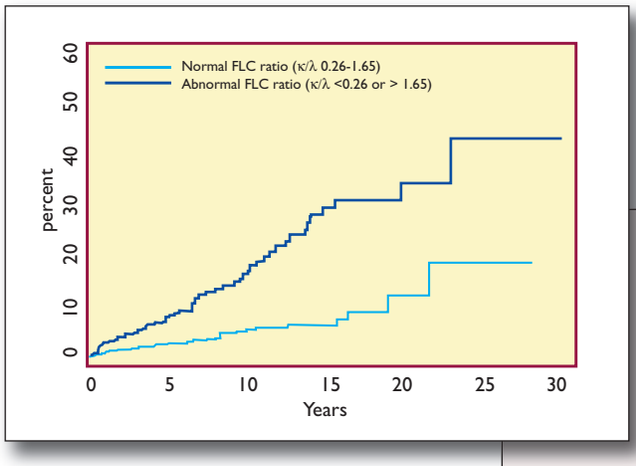
Use Freelite to assess risk of progression in individuals with MGUS and improve their management

MGUS affects some 3% of persons aged 50 years or older.[20] The majority of MGUS patients will not develop MM or a related disorder in their lifetime. However, as approximately 1% of MGUS patients will progress to disease each year, the management of MGUS patients presents a significant challenge to healthcare professionals.
An abnormal serum kappa/lambda FLC ratio has been identified as an independent risk factor for progression of MGUS to MM or related disorders[21] and is represented in the table below describing MGUS risk stratification.

Risk group	N	Absolute risk of progression at 20 years*
Low (serum M protein <15 g/L, IgG subtype, Normal FLC ratio)	449	2%
Low intermediate risk (Any 1 factor abnormal)	420	10%
High intermediate risk (Any 2 factors abnormal)	226	18%
High risk (All 3 factors abnormal)	53	27%

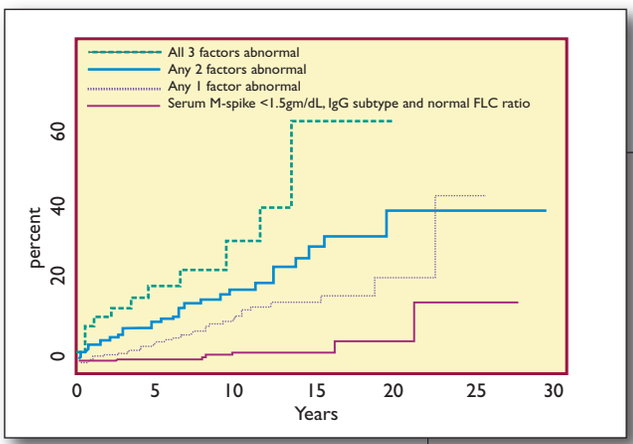
MGUS risk stratification.
N: Number of patients
* accounting for death as a competing risk.

This research was originally published in *Blood.*: Rajkumar *et al*. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005; 106:812-817 ©2005 The American Society of Hematology.



Risk stratification based on Freelite value. The upper curve illustrates risk of progression of MGUS in patients with an abnormal serum kappa/lambda FLC ratio (<0.26 or >1.65). The lower curve illustrates the risk of progression in patients with a normal ratio.

Blood 2005; 106:812-817 ©2005 The American Society of Hematology.[21]



MGUS risk stratification using Freelite & monoclonal protein size and type. Risk of progression of MGUS to myeloma or related disorder using a risk stratification model that incorporates the FLC ratio and the size and type of the serum monoclonal protein.

Blood 2005; 106:812-817 ©2005 The American Society of Hematology.[21]

Peace of mind

Incorporation of **Freelite** into primary screening protocols for the diagnosis of monoclonal gammopathies will:

- Provide important prognostic information in MM, SMM, AL amyloidosis[22] and solitary bone plasmacytoma.[23]
- Allow risk stratification of MGUS patients and enable identification of high risk patients.[21]
- Enhance detection rates of screening protocols.[24,25]
- Facilitate replacement of urine Bence Jones Protein analysis during initial investigations.[10,11]
- Enable you to provide reassurance to low risk MGUS patients which may be 40% of all MGUS patients.[21]
- Enable you to identify high risk patients and monitor them more closely. Risk stratification of MGUS patients with **Freelite** will enable you to allocate resources appropriately.
- Ensure you have all the information to establish the right care plan.

Assess prognosis and deliver the right care plan.

Freelite – Recommended when Monitoring

Monitor more patients accurately and easily

The International Myeloma Working Group (IMWG) guidelines[1] recommend the serial assessment of free light chain (FLC) levels in all patients with AL amyloidosis and in Multiple Myeloma (MM) patients with oligosecretory disease. Additionally they recommend monitoring Intact Immunoglobulin Multiple Myeloma (IIMM) patients periodically to identify light chain (LC) escape. They also recommend use of **Freelite** in all patients who achieve a complete response to determine if there is a stringent complete response.

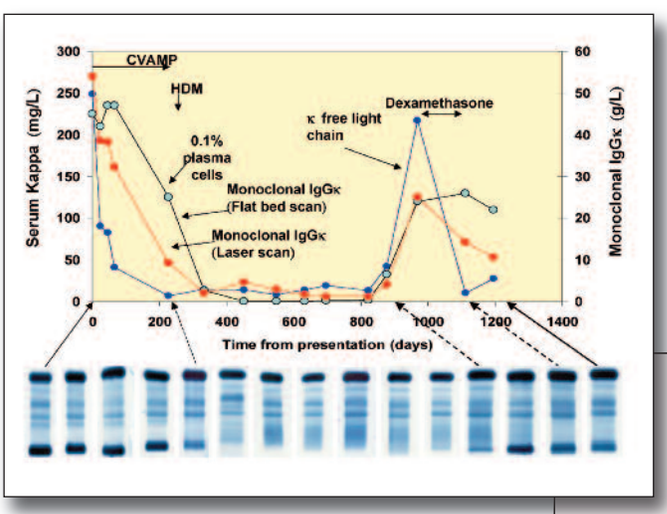
Freelite provides a rapid, quantifiable measure of serum free light chains to aid laboratory monitoring of monoclonal disease states

- Confidently use **Freelite** for monitoring all your MM and AL amyloidosis patients.
- FLC have a half-life of just 2-6 hours in serum and so may reflect responses to treatment in a more timely fashion.
- **Freelite** is highly specific and sensitive for serum kappa and lambda FLC.
- The sensitivity of **Freelite** assays is much greater than currently available urine assays.
- **Freelite** enables you to identify the status of patients even if a different monoclonal protein is produced in relapse.

Intact Immunoglobulin Multiple Myeloma

Measurement of serum FLC with **Freelite** has shown that 96% of patients with IIMM have an abnormal light chain concentration or abnormal kappa/lambda ratios.[6]

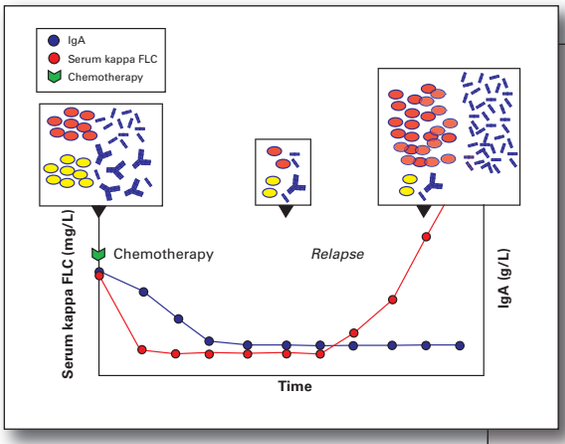
Freelite provides sensitive analysis and is "...a more rapid measure of tumour kill than intact immunoglobulins".[6]



Monitoring of a myeloma patient using IgGκ and free κ. Electrophoresis gels are shown for each sample.

Light Chain Escape

For some IIMM patients relapse is accompanied by a marked rise in monoclonal serum FLC with no associated increase in intact immunoglobulin concentrations. This phenomenon is known as LC escape or Bence-Jones escape.[26]



A model of light chain escape in a hypothetical patient with IIMM.
Dual plasma cell subsets are present at diagnosis producing either monoclonal intact immunoglobulin and FLC or FLC alone. In response to chemotherapy, intact immunoglobulin and serum FLC concentrations fall (FLC fall more rapidly due to their shorter half life). Disease relapse with LC escape is associated with proliferation of the light chain only plasma cell clone but not the intact immunoglobulin producing clone. This leads to a marked rise in serum FLC but no associated change in the intact immunoglobulin concentration.

Why is it important to detect light chain escape early?

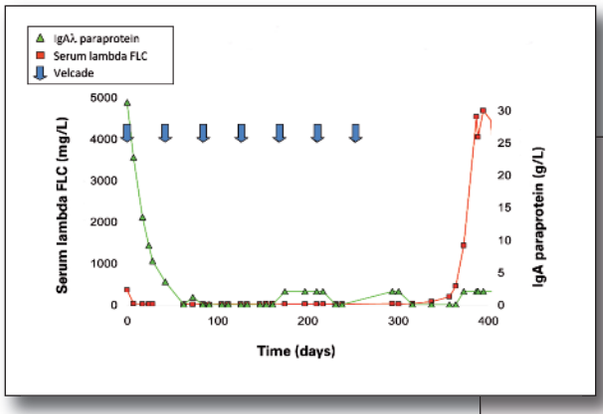
- LC escape is associated with increased tumour growth and is indicative of disease progression[27]
- Patients with LC escape may have a poorer prognosis[26]
- By detecting LC escape early, unnecessary complications such as renal impairment, may be avoided[28]

Light chain escape and its detection may increase with:

- Longer patient survival[29]
- Modern therapies[29]
- Use of serum FLC assay is likely to improve detection rates[29]

Measurement of serum immunoglobulin concentrations will fail to identify LC escape. Without **Freelite**, LC escape is only detectable by urine Bence Jones Protein measurement. Mead *et al.* examined 11 patients identified as showing LC escape; this was corroborated by urine results in 5 of the patients. However, in the other 6 patients the urine FLC were unmeasurable.[30]

Freelite is a reliable measure of disease progression[28] and LC escape may only be detected when monitoring with Freelite.[31]



Courtesy of E. Liakopoulou, Christie Hospital, Manchester, UK

Patient with IgA lambda paraprotein.

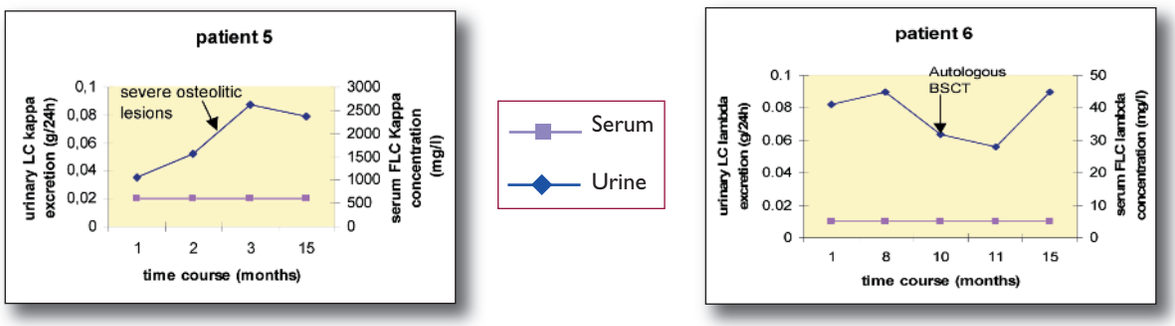
This patient received Velcade® and responded to treatment, both IgA and lambda FLC concentrations fell.

Several months later IgA concentrations remained stable but lambda FLC increased significantly, indicating LC escape.

This case highlights the importance of using Freelite to monitor IIMM patients.

Light Chain Multiple Myeloma

The serum Freelite assay is sensitive enough for correlation with clinical events and is more sensitive than urine results.



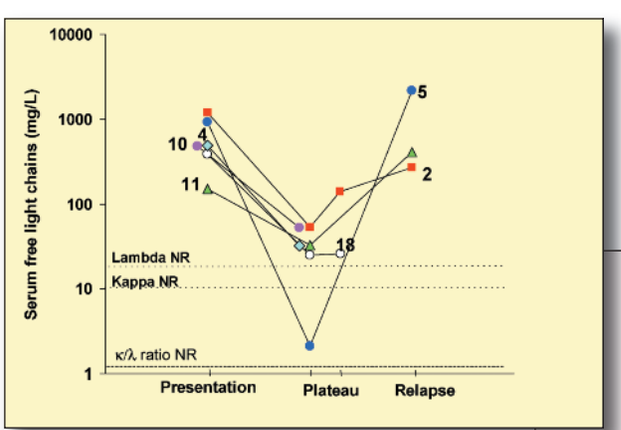
Alyanakian *et al.*[32] concluded:

"Immunonephelometric measurement of serum free light chains are a reliable method for follow up of patients with light chain secreting monoclonal gammopathies". Also that for cases featuring hardly measurable amounts of light chain in the urine *"...the serum free light chain assay proved sensitive enough for correlation with clinical events."*

Nonsecretory Multiple Myeloma

- Most Nonsecretory Multiple Myeloma (NSMM) patients can now be monitored simply, using a serum sample.
- **Freelite** improves the precision of monitoring patients with NSMM compared to traditional methods.
- Monitor the majority of NSMM patients without compromise.
- The number of bone marrow biopsies for this group of patients can be reduced.
- Reduce patient anxiety with fewer bone marrow biopsies.

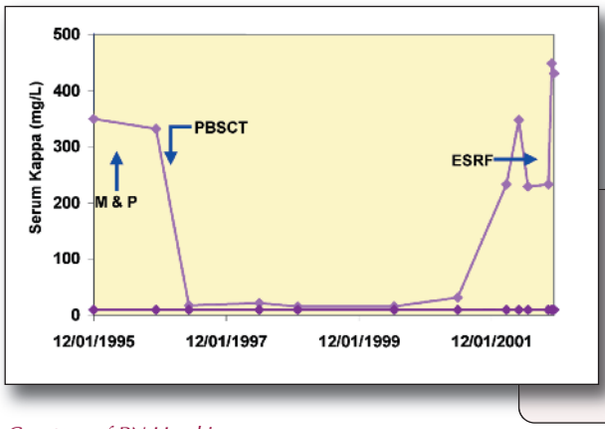
Freelite detected abnormal serum FLC in 82% of patients previously classified as non secretors by conventional methods. The sensitivity of **Freelite** can help to detect and monitor these patients effectively.



Changes in serum FLC concentrations and clinical status in 6 patients with NSMM[4] can readily be seen using Freelite.
NR=Upper limit of normal range

AL amyloidosis

Measurement of serum FLC with **Freelite** has been shown to clearly follow the course of disease whilst the monoclonal IgG kappa, detectable by immunofixation electrophoresis, remained unchanged.[9]



Changes in serum monoclonal proteins during the disease course of a patient with AL amyloidosis.
M&P: melphalan & prednisolone; PBSCT: peripheral blood stem cell autograft; ESRF: end stage renal failure.

Courtesy of PN Hawkins.

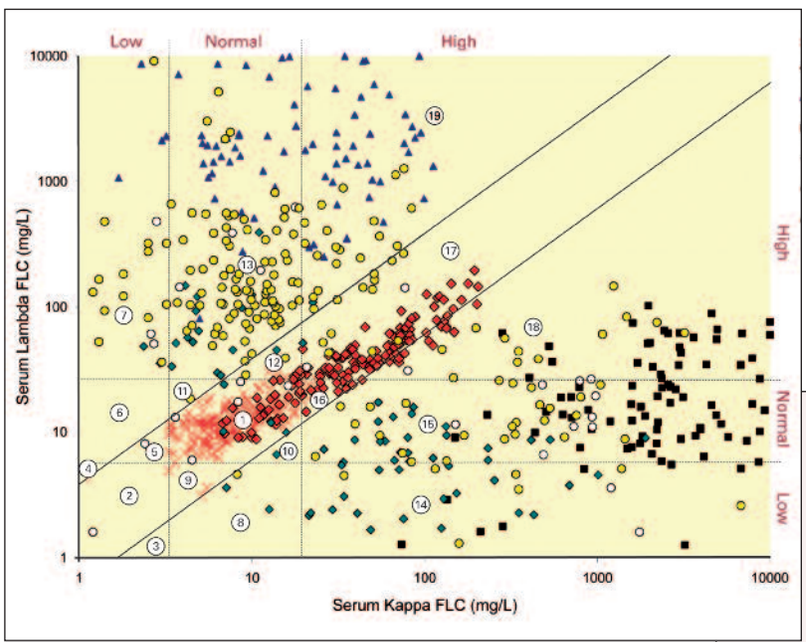
Peace of mind

- **Freelite** can be used to monitor the majority of MM and AL amyloidosis patients offering improved patient management.
- **Freelite** may be useful when there are low concentrations of intact immunoglobulin which makes measurement unreliable.
- **Freelite** allows prompt identification and treatment of relapsing IIMM patients with light chain escape.
- **Freelite** is a sensitive marker of residual disease.
- **Freelite** enables earlier identification of plateau stage.
- **Freelite** provides early indication of resistance to treatment.
- **Freelite** helps minimise patients' exposure to chemotherapy.
- **Freelite** assay time is less than 20 minutes, facilitating rapid clinical decisions.

A vital tool you can't afford to be without.

Interpretation of Results

Results from serum free light chain (FLC) analysis can be plotted on a Dot Plot graph like the one below which shows the serum κ and λ FLC concentrations in a selection of clinical conditions.



Dot Plot
Diagonal lines separate monoclonal from polyclonal FLC production.
Normal ranges for κ, λ (and κ/λ ratio - diagonal lines) are shown.
Sector numbers refer to table 2 below.

The table below (Table 2) gives an indication of interpretation based on which sector the FLC result lies in.

Sector	Kappa	Lambda	κ/λ Ratio	Interpretation
1	Normal	Normal	Normal	Normal serum
2	Low	Low	Normal	BM suppression without MG
3			High	Monoclonal Gammopathy
4			Low	
5		Normal	Normal	Normal serum
6			Low	Monoclonal Gammopathy
7		High	Low	
8	Normal	Low	High	
9			Normal	Normal serum
10		Normal	High	Monoclonal Gammopathy
11			Low	
12		High	Normal	plg or renal impairment
13			Low	Monoclonal Gammopathy
14	High	Low	High	Monoclonal Gammopathy
15		Normal	High	Monoclonal Gammopathy
16			Normal	plg or renal impairment
17		High	Normal	
18			High	MG with renal impairment
19			Low	

With bone marrow (BM) suppression

Without bone marrow (BM) suppression

Table 2.
MG = Monoclonal Gammopathy
plg = Polyclonal Immunoglobulin

Sectors refer to areas of the kappa/lambda plot

Freelite results should be considered under the following categories and investigated appropriately:

1. Normal samples. Serum κ, λ and κ/λ ratio are all within the normal ranges. If accompanying serum electrophoretic tests are normal it is most unlikely that the patient has a monoclonal gammopathy.

2. Abnormal κ/λ ratios. Support the diagnosis of a monoclonal gammopathy and require further investigation. Borderline elevated κ/λ ratios occur with renal impairment and may require appropriate renal function tests.

3. Low concentrations of κ, λ or both. Indicate bone marrow suppression.

4. Elevated concentrations of both κ and λ with a normal κ/λ ratio may be due to the following:

- Renal impairment (common)
- Over-production of polyclonal FLC from inflammatory conditions (common)
- Biclonal gammopathies of different FLC types (rare)

5. Elevated concentrations of both κ and λ with an abnormal κ/λ ratio suggest a combination of monoclonal gammopathy and renal impairment.

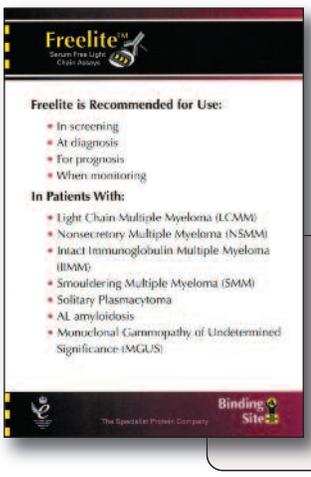
Serum reference ranges

The most extensive serum free light chain normal range study has been conducted at Mayo Clinic, USA, using Binding Site **Freelite** assays for BN™II. In this study serum samples from 282 normal subjects aged from 21 to 90 years were assayed for free kappa and free lambda. The results from this trial are shown in the table below.

Normal Adult Serum	Mean Concn.	Median Concn.	95 %ile Range
Free kappa	8.36 (mg/L)	7.30 (mg/L)	3.30-19.40 (mg/L)
Free lambda	13.43 (mg/L)	12.40 (mg/L)	5.71-26.30 (mg/L)
	Mean	**Median**	**Total range**
Kappa/lambda ratio	0.63	0.60	0.26-1.65

Katzmann JA, *et al.* Serum Reference Intervals and Diagnostic Ranges for Free κ and Free λ Immunoglobulin Light Chains: Relative Sensitivity for Detection of Monoclonal Light Chains. *Clin Chem* 2002; 48:1437-1444

Normal reference range
In most myeloma patients this reference range is used but Binding Site recommends interpreting serum FLC results in the context of renal function. In patients with renal impairment a modified renal reference range for the κ/λ ratio is 0.37 - 3.1.[37]



Pocket guide
This information is also available in a handy pocket guide (request code MKG325.3) which you can keep close to hand.
This pocket guide is also available in other languages. Please ask your local representative for details.

Carry your pocket guide to aid in interpretation.

New hope for Myeloma Kidney patients

The majority of patients with Multiple Myeloma (MM) produce an excess of free light chains (FLC) which contribute to the development of renal impairment in up to 50% of myeloma patients.[33] Some 20% of myeloma patients will develop rapidly progressive renal failure.[34] This is reported to result in around 1-12% of all patients with myeloma requiring dialysis.[34,35,36] Myeloma patients who have renal failure have a worse prognosis. This is partially due to the requirement for chronic dialysis which has a profound effect on long-term outcome.[36] The most common cause of acute renal failure, in myeloma patients, is cast nephropathy (also known as "myeloma kidney"). See Figure 1, below.

Add **Freelite** to your algorithm for a more sensitive and specific protocol to rapidly detect B cell dyscrasias.

Helping to protect the kidneys requires:

- Recognition of myeloma as a potential cause
- Rapid identification of patients at risk
- Early detection of kidney damage
- Rapid removal of FLC

Rapid identification

Freelite enables the accurate quantification of circulating nephrotoxic FLC levels directly in the serum sample.
The combination of serum protein electrophoresis (SPE) and **Freelite** is the most simple and efficient initial diagnostic screen for the detection of high tumour burden monoclonal gammopathies.[2]

Freelite is readily available from the laboratory in the same way as traditional electrophoretic assays; request **Freelite** when you order a SPE. **Freelite** is a proven aid in the diagnosis of monoclonal gammopathies and is recommended by International guidelines for the diagnosis, screening and monitoring of monoclonal gammopathies.[1]

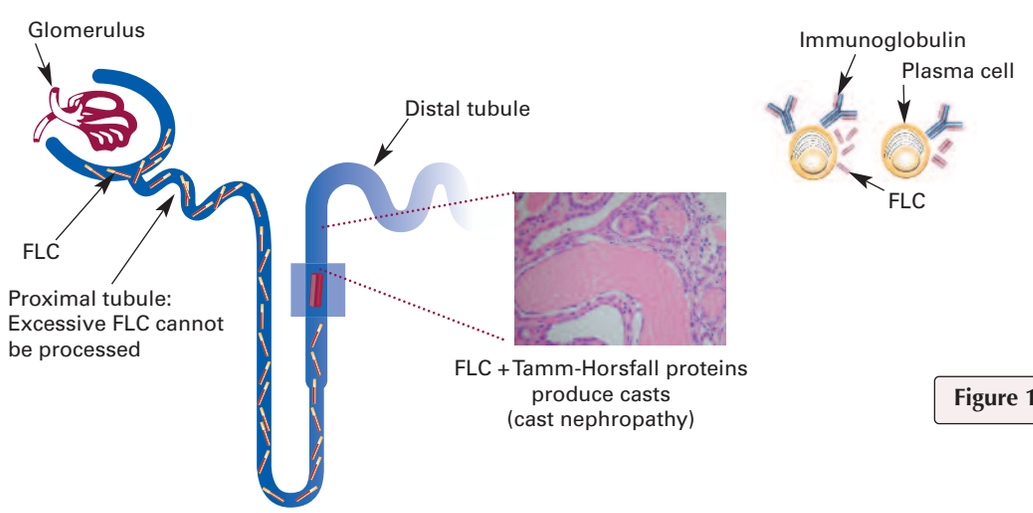
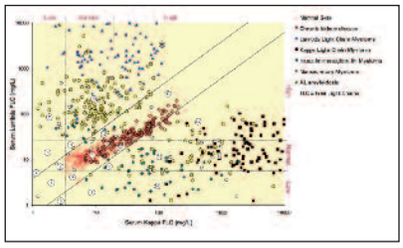


Figure 1.

Interpretation

Freelite is a sensitive specific marker of kappa and lambda FLC in serum and provides quantitative measurement of serum free kappa, serum free lambda and the serum free kappa/lambda ratio.
The serum FLC ratio is a highly sensitive indicator of monoclonality and will detect many patients missed by electrophoretic assays. **Freelite** results, used in conjunction with renal function tests, can help distinguish a polyclonal from a monoclonal response.



Freelite results can be plotted on a Dot Plot as shown here and in more detail on page 14.

Normal Adult Serum	Mean Concn.	Median Concn.	95 %ile Range
Free kappa	8.36 (mg/L)	7.30 (mg/L)	3.30-19.40 (mg/L)
Free lambda	13.43 (mg/L)	12.40 (mg/L)	5.71-26.30 (mg/L)
	Mean	**Median**	**Total range**
Kappa/lambda ratio	0.63	0.60	0.26-1.65

Katzmann JA, *et al.* Serum Reference Intervals and Diagnostic Ranges for Free κ and Free λ Immunoglobulin Light Chains: Relative Sensitivity for Detection of Monoclonal Light Chains. *Clin Chem* 2002; 48:1437-1444

Normal reference range
In most myeloma patients this reference range is used but Binding Site recommends interpreting serum FLC results in the context of renal function. In patients with renal impairment a modified renal reference range for the κ/λ ratio is 0.37 - 3.1.[37]

Rapid removal: A new choice for Myeloma Kidney Therapy

Traditional treatments are not the answer

At present, myeloma kidney patients are treated through attempts to remove FLC plasma exchange is a logical approach, but shows no clinical benefit.[38] A 3.5L plasma exchange removes 65% of intravascular FLC but has very little impact on overall FLC levels. This is because FLC are present in a larger volume in the extravascular compartment (approximately 80% of the total) and tissue oedema fluid. On the whole, dialysers are similarly ineffective when used to remove FLC and do not clear sufficient quantities to offer any real benefit to the patient.[39]

An improved choice

A new therapy for myeloma kidney patients is now available; it is an innovative new product from Gambro® called **Theralite™** High Cut-off technology. **Freelite** can be used to assess the efficiency of the membrane to enable sufficient removal to restore kidney function.

Peace of mind

- **Freelite** offers improved sensitivity to prevent missed myeloma patients.
- **Freelite** is a simple laboratory test that is performed on serum so is not affected by renal function.
- **Freelite** can be used to assess the efficiency of light chain removal techniques.
- **Freelite** directly measures the nephrotoxic FLC itself.

A new lifeline for myeloma kidney patients.

Who benefits from use of Freelite?

Patients: Reassurance

- A simple blood test; no need for 24 hour urines
- Potential earlier diagnosis
- Reassurance for MGUS patients[1,21]
- Improved monitoring of disease activity
- "..more rapid measure of tumour kill than intact immunoglobulins"[6]
- "An early indication of resistance to treatment would allow the administration of ineffective chemotherapy drugs to be minimized"[6]
- Nonsecretory Multiple Myeloma patients can be included in clinical trials[40] and no longer need to be monitored by serial bone marrow biopsies[4]

Clinicians: Peace of mind

- Proven as an aid to the diagnosis of Multiple Myeloma (MM)
- Detect 100% of Light Chain MM with serum FLC assays[3]
- Detect 82% of Nonsecretory MM with serum FLC assay[4]
- Detect 98% of AL amyloidosis with serum FLC assays[5]
- Compliance to International guidelines[1]
- Essential for classification of stringent complete response[40]
- "The short half-life of kappa* allows it to mirror the kinetics of tumor kill in contrast to intact IgG, which is insensitive to different kill rates. The rate and depth of fall…..may rapidly indicate the need for further treatment or a change in treatment."[41]
- "An early indication of resistance to treatment would allow the administration of ineffective chemotherapy drugs to be minimized and be a valuable aid when selecting treatment regimens."[6]

Laboratory: Increased Efficiency

- Improve detection of B cell dyscrasias by 56%[24]
- **Freelite** & SPE provide 100% sensitivity & 100% negative predictive value at diagnosis[25]
- Sensitive indicator of monoclonality[3]
- Serum analysis on a wide range of automated platforms
- Quantitative result enabling auto-validation
- Improved turn-around time[10]
- Replacement of urine assays in the diagnosis of MM[2,11]
- Greater sensitivity than urine IFE[13]
- Compliance to International guidelines[1]

Administration: Cost Effectiveness

- Reduced risk of misdiagnosing MM patients[24,10,25]
- "An early indication of resistance to treatment would allow the administration of ineffective chemotherapy drugs to be minimized……"[6]
- Reduce or replace expensive and time-consuming urine tests[10]
- Appropriate resource allocation for MGUS patients
- Compliance to International guidelines[1]

*Half-life 2-4 hours; 3-6 hours

Have you also considered Freelite for use in:

- B-cell Chronic Lymphocytic Leukaemia
- Diffuse large B-cell Lymphoma
- HIV and Lymphoma development
- HCV and Lymphoma development
- Sjögren's Syndrome
- Hodgkin's Lymphoma
- Non-Hodgkin's Lymphomas

A number of studies using **Freelite** for a range of other diseases are being conducted. Ask your sales representative for more information including the latest publications on these applications.

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Binding Site is a Specialist Protein company. It is committed to the research, development, manufacture and distribution of innovative immunodiagnostic assays for the global laboratory market. With extensive expertise in antibody specificity technology, Binding Site gives clinicians and laboratory staff the tools to significantly improve diagnosis and management of patients across a range of cancers and immune system disorders.

World-wide support is provided from Binding Site offices for customers in the UK (head office), USA, Canada, Germany, Austria, France, Spain, Czech Republic, Slovac Republic, Belgium, Netherlands and Luxembourg and by an extensive network of experienced distributor companies in a further 80 countries.

Freelite & **Hevylite™** Milestones

2000 Launch of **Freelite** serum free light chain assays.

2001 First publication highlighting the clinical significance of **Freelite** in Nonsecretory Multiple Myeloma patients is published in *Blood*.

2003 Publication highlighting the clinical utility of **Freelite** for the replacement of Bence Jones Protein in *The Lancet*.

2004 First National guidelines for the incorporation of **Freelite** assays into the management of Primary Amyloidosis patients published in the *British Journal of Haematology*.

2005 International Consensus on **Freelite** assays for AL amyloidosis published in *American Journal of Hematology*.

2006 **Freelite** incorporated into the National UK guidelines for the diagnosis and monitoring of Multiple Myeloma published in the *British Journal of Haematology*.

2006 **Freelite** incorporated into new International uniform response criteria for Multiple Myeloma published in *Leukemia*.

2006 Mayo Clinic publish the first independent study in the USA recommending **Freelite** as a routine screening test in *Mayo Clinic Proceedings*.

2007 Binding Site won Queen's Award for Enterprise in the category Innovation, for the **Freelite** serum free light chain assay.

2007 *Journal of the American Society of Nephrology* publishes the first study using Haemodialysis for the removal of serum free light chains as measured by **Freelite**.

2007 Clinical utility of **Freelite** for prognosis of Multiple Myeloma published in *Blood* and *British Journal of Haematology*.

2007 First Binding Site SPAPLUS™ automated analyser placed in US Cancer Centre to run **Freelite** assays.

2008 Launch of EuLITE clinical trial using velcade-based chemotherapy and haemodialysis for the removal of serum free light chains as measured by **Freelite**.

2008 International Myeloma Working Group publish recommendations for use of **Freelite** in screening, prognosis and treatment response in *Leukemia*.

2009 Launch of **Hevylite**.

2009 First publication highlighting the clinical significance of **Hevylite** in *Clinical Chemistry*.

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