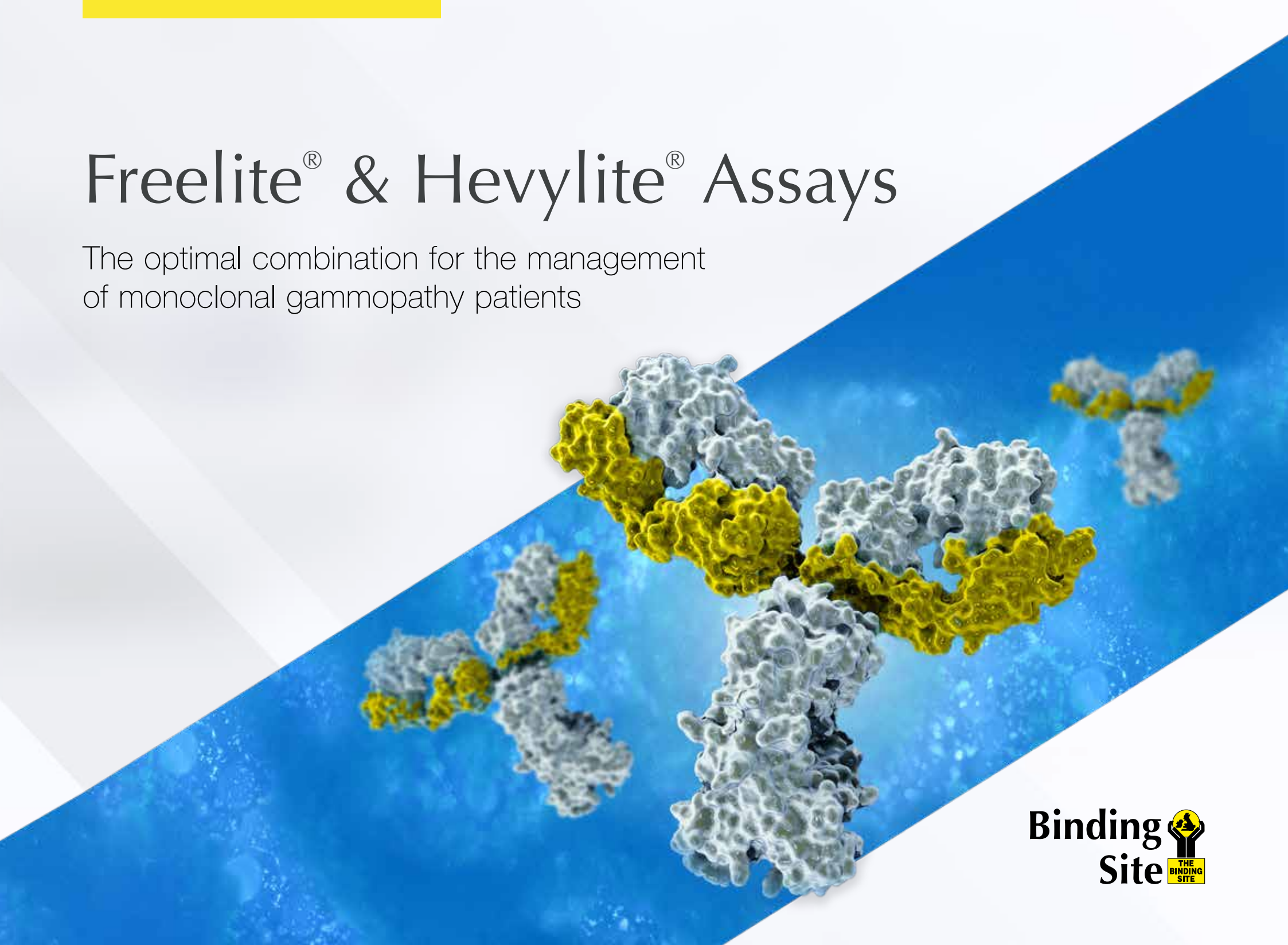
Freelite® & Hevylite® Assays

The optimal combination for the management of monoclonal gammopathy patients

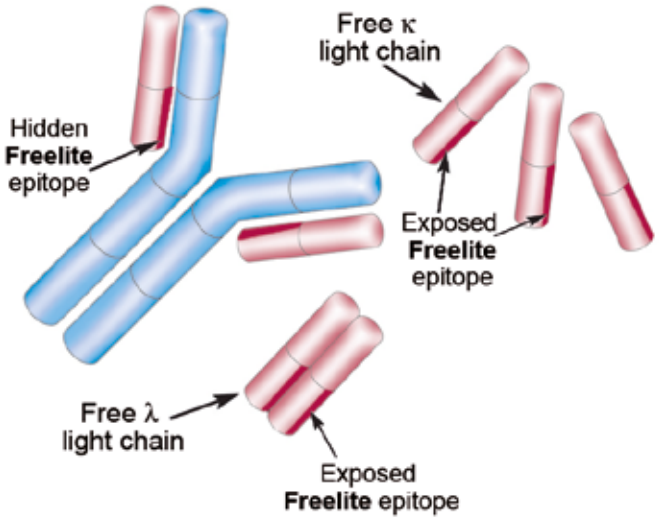


Binding Site

Freelite assays

The **Freelite** assays are two sensitive and specific polyclonal immunodiagnostic tests to measure κ and λ FLCs in serum.

The κ/λ FLC ratio is a sensitive marker of light chain clonality.

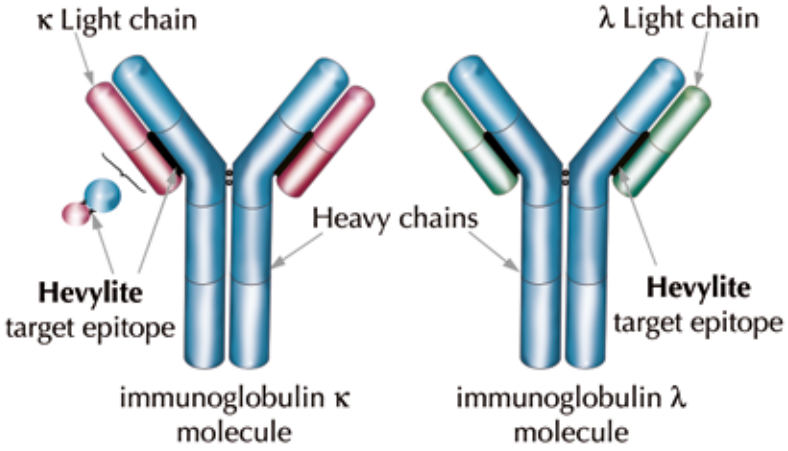


Freelite assays are the only FLC tests recommended by both national and international guidelines.

Hevylite assays

Hevylite assays identify and quantify individual heavy + light chain (HLC) isotypes, i.e. IgGκ, IgGλ, IgAκ, IgAλ, IgMκ and IgMλ.

These molecules are measured in pairs, e.g. IgGκ/IgGλ, to produce ratios in the same manner as the κ/λ sFLC ratio.



The **Hevylite** assay works by targeting epitopes between the heavy chain and light chain constant regions.

" The HLC assays allow new ways to examine plasma cell biology and disease. We are able to identify abnormalities that were previously hidden from our view..."[1]

Improve your accuracy in detecting monoclonal gammopathies

FLC = Free Light Chain sFLC = Serum Free Light Chain HLC = Heavy + light chain isotypes

Freelite and Hevylite assays in Monoclonal Gammopathy testing

Diagnosis

Multiple Myeloma

- **Freelite** assays determine a “myeloma defining event”*
- **Freelite** assays and SPE are an efficient aid in screening and diagnosis
- **Freelite** assays are recommended to rule out cast nephropathy

MGUS

- **Freelite** and **Hevylite** assays for risk stratification and prognosis

Monitoring

Clonal change

- **Freelite** and **Hevylite** assays measure two independent biomarkers
- **Freelite** and **Hevylite** assays to follow clonal change
- **Freelite** assays to detect light chain escape

Difficult to measure monoclonal proteins

- **Freelite** and **Hevylite** assays to monitor oligosecretory MM
- **Freelite** assays to monitor LCMM, NSMM and AL amyloidosis
- **Hevylite** assays to monitor when electrophoresis is inaccurate or insensitive

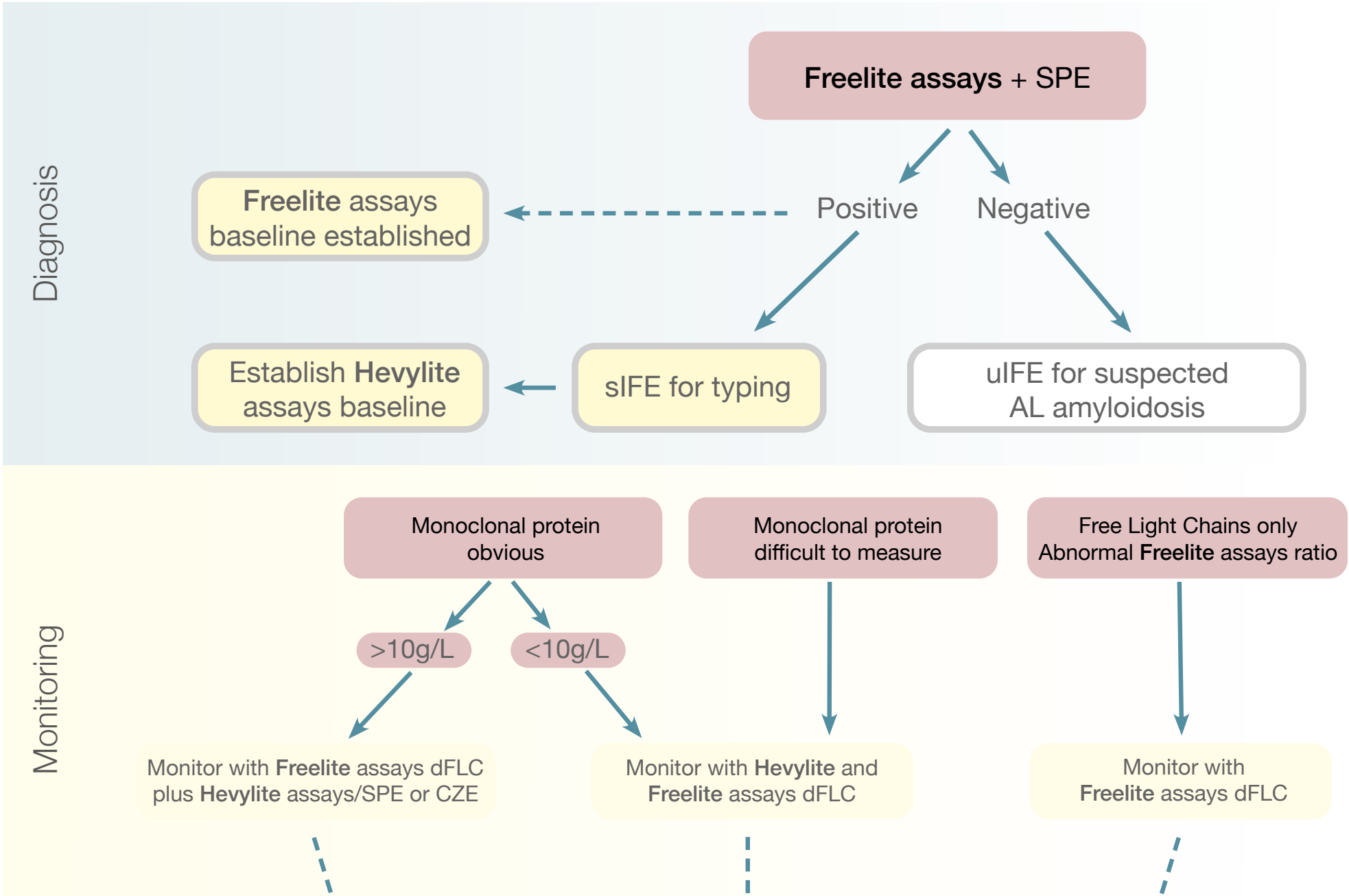
Residual Disease

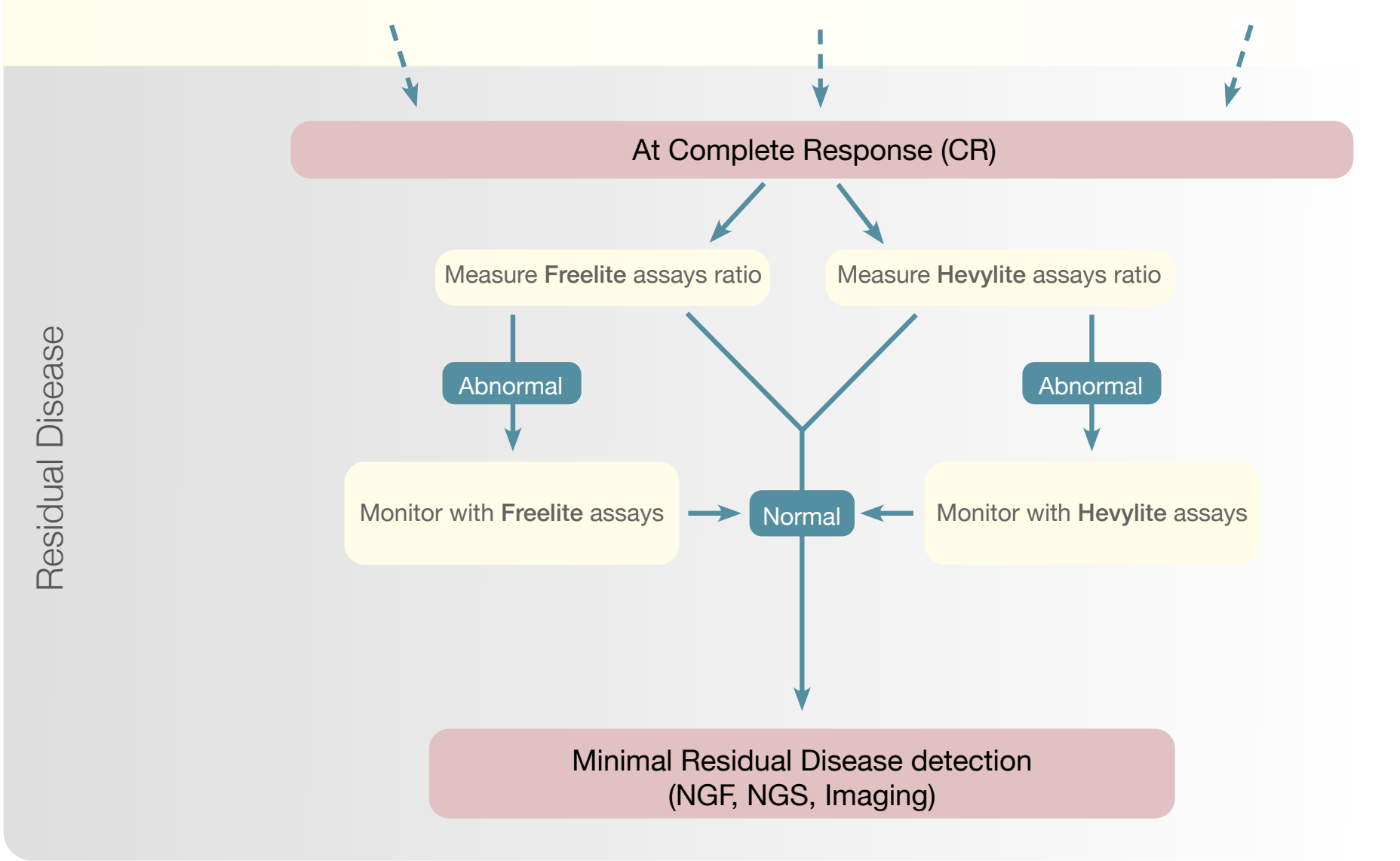
Depth of response

- **Freelite** and **Hevylite** assays capture more residual disease
- **Freelite** and **Hevylite** assays as gateway tests to MRD analysis
- **Freelite** assays to define stringent complete response

SPE = Serum Protein Electrophoresis MGUS = Monoclonal Gammopathy of Undetermined Significance MM = Multiple Myeloma LCMM = Light Chain Multiple Myeloma
NSMM = Nonsecretory Multiple Myeloma MRD = Minimal Residual Disease * Involved/uninvolved sFLC ratio ≥100 and involved Freelite ≥100mg/L

Freelite and Hevylite in the management of Monoclonal Gammopathies





SPE = Serum Protein Electrophoresis sIFE = serum Immunofixation Electrophoresis dFLC = involved Free Light Chain - uninvolved Free Light Chain
uIFE = urine Immunofixation Electrophoresis NGS = Next Generation Sequencing NGF = Next Generation Flow Cytometry CZE = Capillary Zone Electrophoresis

Diagnosis

IMWG Guidelines for Diagnosis of Multiple Myeloma

IMWG Criteria for MM diagnosis[2]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and one or more myeloma defining events:

One or more biomarkers of malignancy (**SLiM**)

- Clonal bone marrow plasma cells ≥60% (**S**ixty %)
- **Involved/uninvolved serum Free Light Chain ratio ≥100***
- >1 focal lesion on **M**RI studies

* By Freelite (iFLC must be ≥100mg/L)

OR

Related end organ damage (**CRAB**)

- Hyper**C**alcaemia
- **R**enal insufficiency
- **A**naemia
- **B**one lesions

Freelite forms part of the IMWG diagnostic criteria for MM

IMWG = International Myeloma Working Group MM = Multiple Myeloma MRI = Magnetic Resonance Imaging

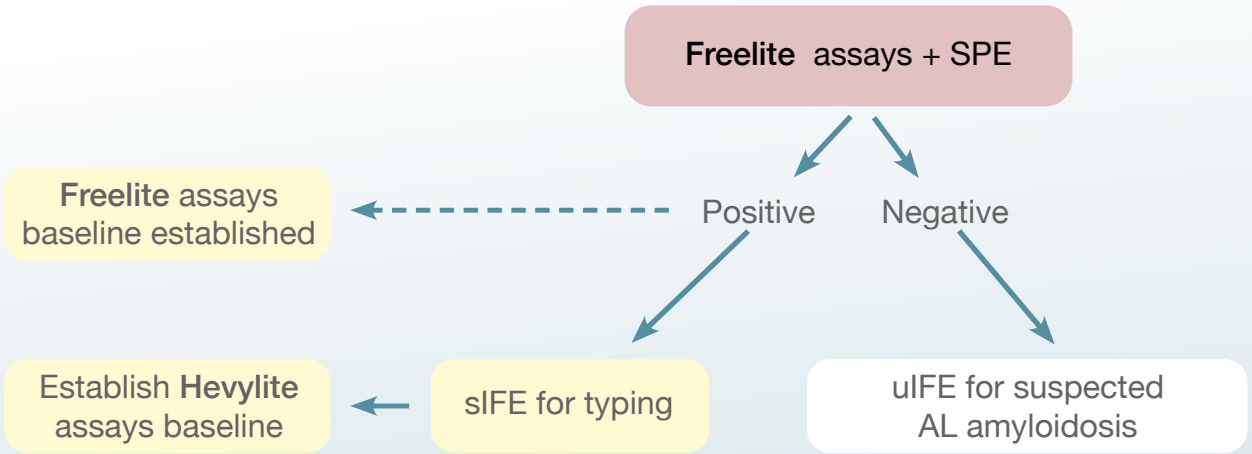
Use Freelite and Hevylite together

The IMWG guidelines recommend **Freelite** assays for the diagnosis of monoclonal gammopathies.[3] The assay quantitatively measures free light chains providing improved accuracy compared to traditional methods.

Freelite assays should be used with SPE in the initial testing of patients to detect monoclonal gammopathies, allowing urine testing to be used more selectively.[3,4]

Hevylite assay results provide a baseline value that is useful in monitoring and prognosis. It can also help to clarify problematic SPE results.

At Diagnosis



Diagnose more monoclonal gammopathies with Freelite and Hevylite assays

IMWG = International Myeloma Working Group SPE = Serum Protein Electrophoresis sIFE = serum Immunofixation Electrophoresis
uIFE = urine Immunofixation Electrophoresis

Optimising your Diagnostic Approach for Monoclonal Gammopathy Testing

A combination of **Freelite** assays and SPE is a clinically sensitive strategy for diagnosis of monoclonal gammopathies[4].

Protocols	% of Paraproteins detected			
	*Myeloma[4]	AL amyloidosis[4]	LCMM[5,6,7]	NSMM[8]
SPE alone	88	66	40 - 57	0
Serum IFE	94	74	n.d.	0
SPE, serum IFE, urine IFE	100	94	n.d.	0
SPE/CZE and **Freelite** assays	100	96	100	68
SPE/CZE, **Freelite** assays and serum IFE	100	97	100	68

** Myeloma is inclusive of 467 patients with MM (451), NSMM (4), Plasma cell leukaemia (4), Osteosclerotic MM (1), and Indolent Myeloma (7).*

NICE Guidelines recommend SPE and sFLC assessment to screen for monoclonal protein in patients with suspected myeloma

"urine testing was only done in a fraction of the people being tested. This could have resulted in potential missed diagnoses if the sFLC test was not performed as an alternative" [9]

Detect more monoclonal gammopathies with Freelite assays as recommended by IMWG

SPE = Serum Protein Electrophoresis IFE = Immunofixation Electrophoresis n.d. = no data CZE = Capillary Zone Electrophoresis sFLC = Serum Free Light Chain
LCMM = Light Chain Multiple Myeloma NSMM = Nonsecretory Multiple Myeloma NICE = National Institute for Health and Care Excellence (UK)
IMWG = International Myeloma Working Group

MGUS risk stratification improves patient management

Risk stratification is recommended for all MGUS patients to optimise counselling and follow-up, based on three independent risk factors:[10]

1. Abnormal κ/λ sFLC ratio
2. Serum monoclonal protein ≥15 g/L
3. IgA or IgM type

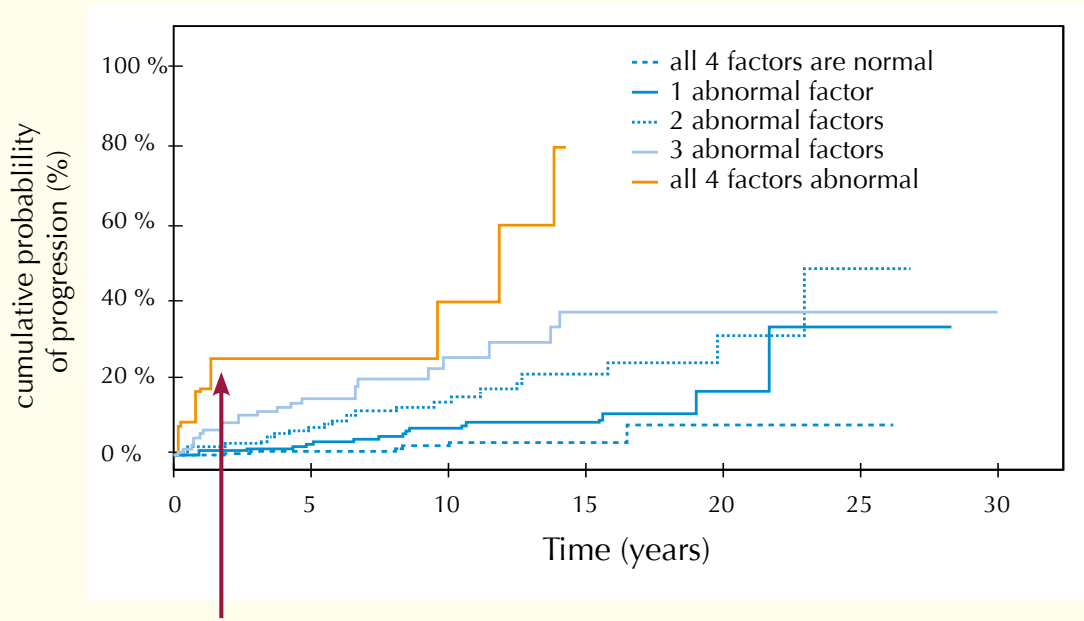
Extended risk stratification:[11]

4. **Hevylite** assays (HLC) pair suppression*

Hevylite assays pair suppression is a new, independent biomarker for identifying MGUS patients at high risk of malignant progression.

*When the concentration of the uninvolved HLC is below the normal reference interval, provided the HLC ratio is abnormal.

MGUS risk stratification using 4 risk factors



25% of patients with 4 risk factors developed MM or a related condition within two years.[11]

Freelite & Hevylite assays allow optimal risk stratification of MGUS patients

sFLC = serum Free Light Chain HLC = Heavy + light chain isotypes MGUS = Monoclonal Gammopathy of Undetermined Significance MM = Multiple Myeloma

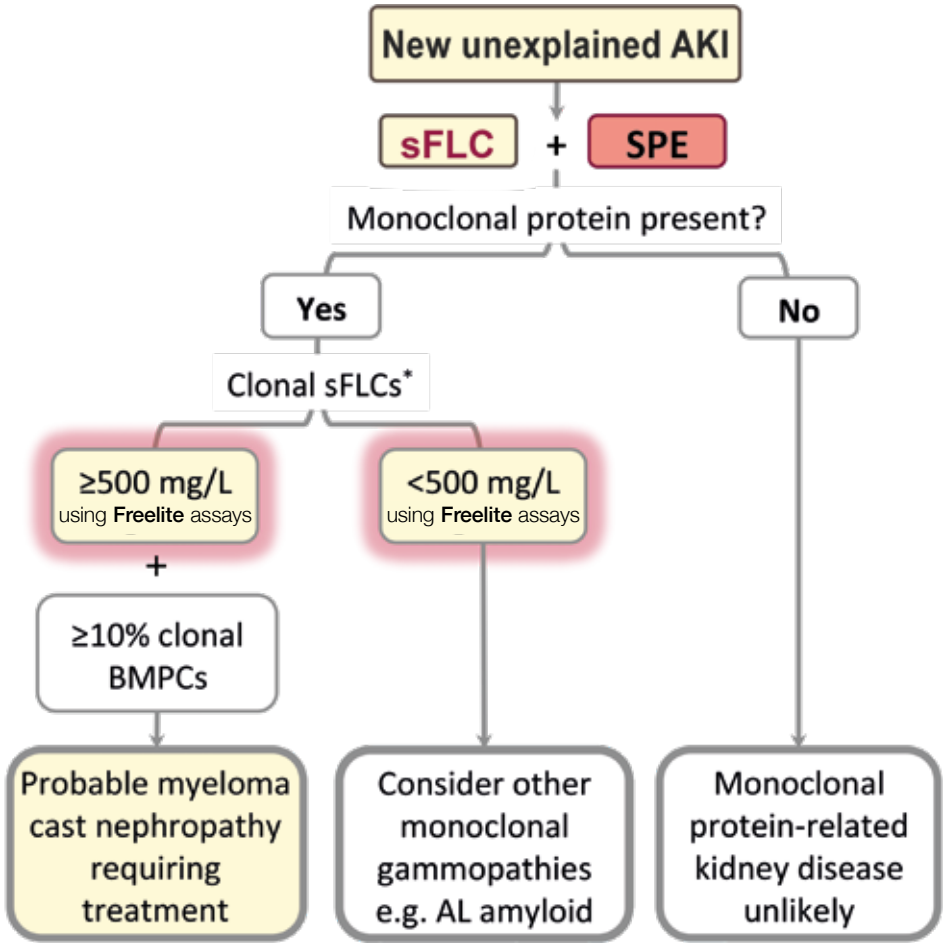
Detect Myeloma Kidney early to increase the chance of renal recovery

Up to 45% of newly diagnosed myeloma patients will have renal insufficiency, 20% will have severe renal impairment and 3.5% will have renal failure requiring dialysis.[12]

90% of renal failure in multiple myeloma is due to cast nephropathy (myeloma kidney).[13]

Irreversible kidney damage can be prevented by early detection of nephrotoxic monoclonal FLCs using **Freelite** assays, followed by myeloma treatment.

The International Kidney and Monoclonal Gammopathy Research Group recommend sFLC analysis for the investigation of new, unexplained AKI.[14]



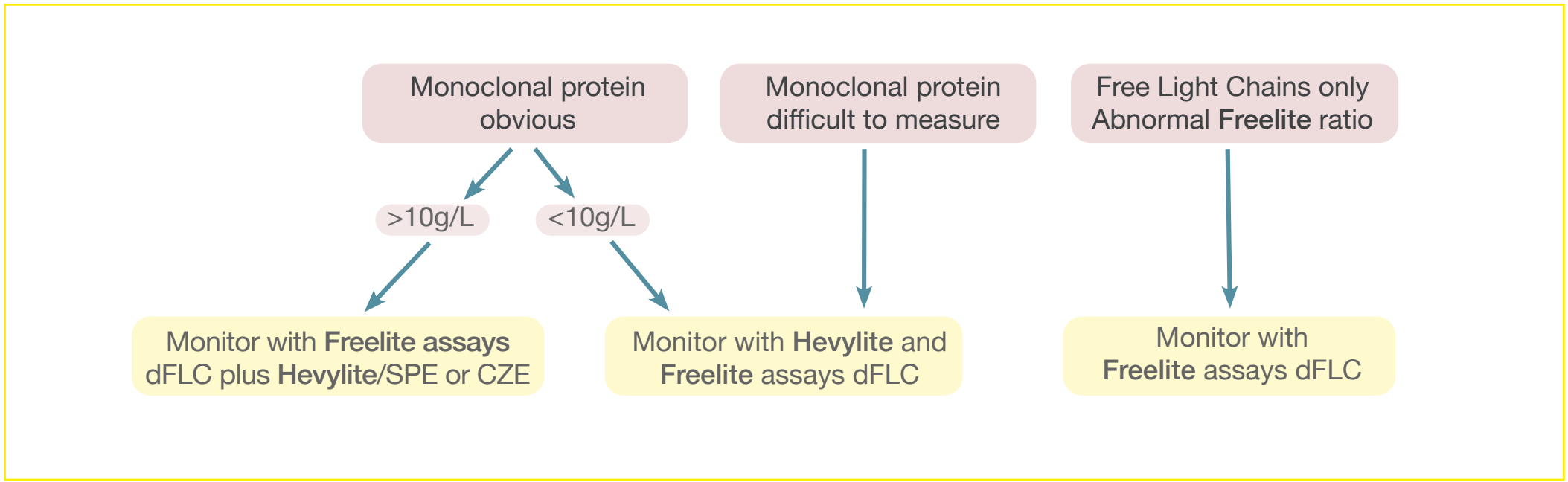
* Positive = k/l ratio outside 0.37 - 3.1

Rapid diagnosis & treatment is essential for improving outcomes in cast nephropathy

AKI = Acute Kidney Injury FLCs = Free Light Chains sFLC = serum Free Light Chains SPE = Serum Protein Electrophoresis BMPCs = Bone Marrow Plasma Cells

Monitoring

Use Freelite and Hevylite assays together for optimal management of Multiple Myeloma patients



Use Freelite and Hevylite assays together:

- To quantitatively monitor patients with Multiple Myeloma
- To identify clonal change

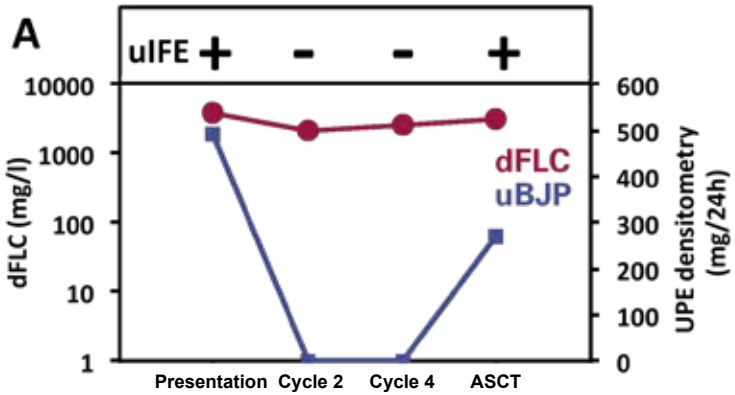
SPE = Serum Protein Electrophoresis CZE = Capillary Zone Electrophoresis dFLC = involved Free Light Chain minus the uninvolved Free Light Chain

Serum Freelite assay results provide more accurate information than urine BJP

Shown here are two Light Chain Multiple Myeloma patients being monitored by serum **Freelite** assays (shown in **red**) and UPE (uBJP - shown in **blue**).

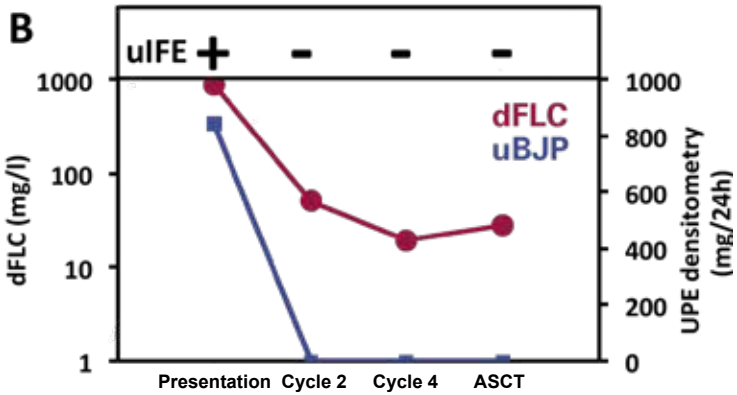
In both cases, measurement of uBJP overestimates the response to treatment but **Freelite** assays correctly indicate residual disease.[15]

A: κ FLC patient

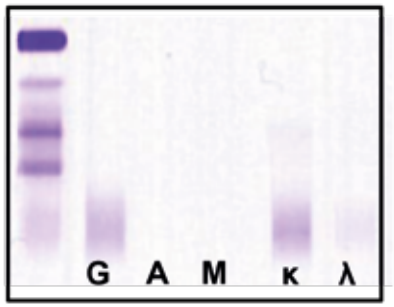


dFLC indicates no response to therapy where UPE and uIFE become negative at cycle 2.

B: λ FLC patient

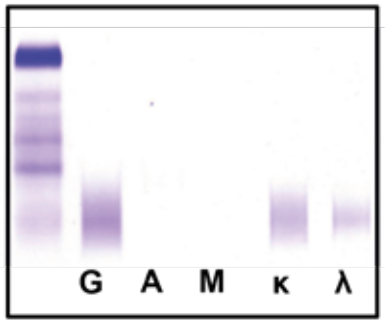


dFLC indicates a VGPR (very good partial response) at the end of cycle 2 and presence of residual disease whereas UPE and uIFE became negative and yielded no information on residual disease.



sIFE confirmed the presence of residual disease.

sIFE Cycle 2



sIFE confirmed the presence of residual disease.

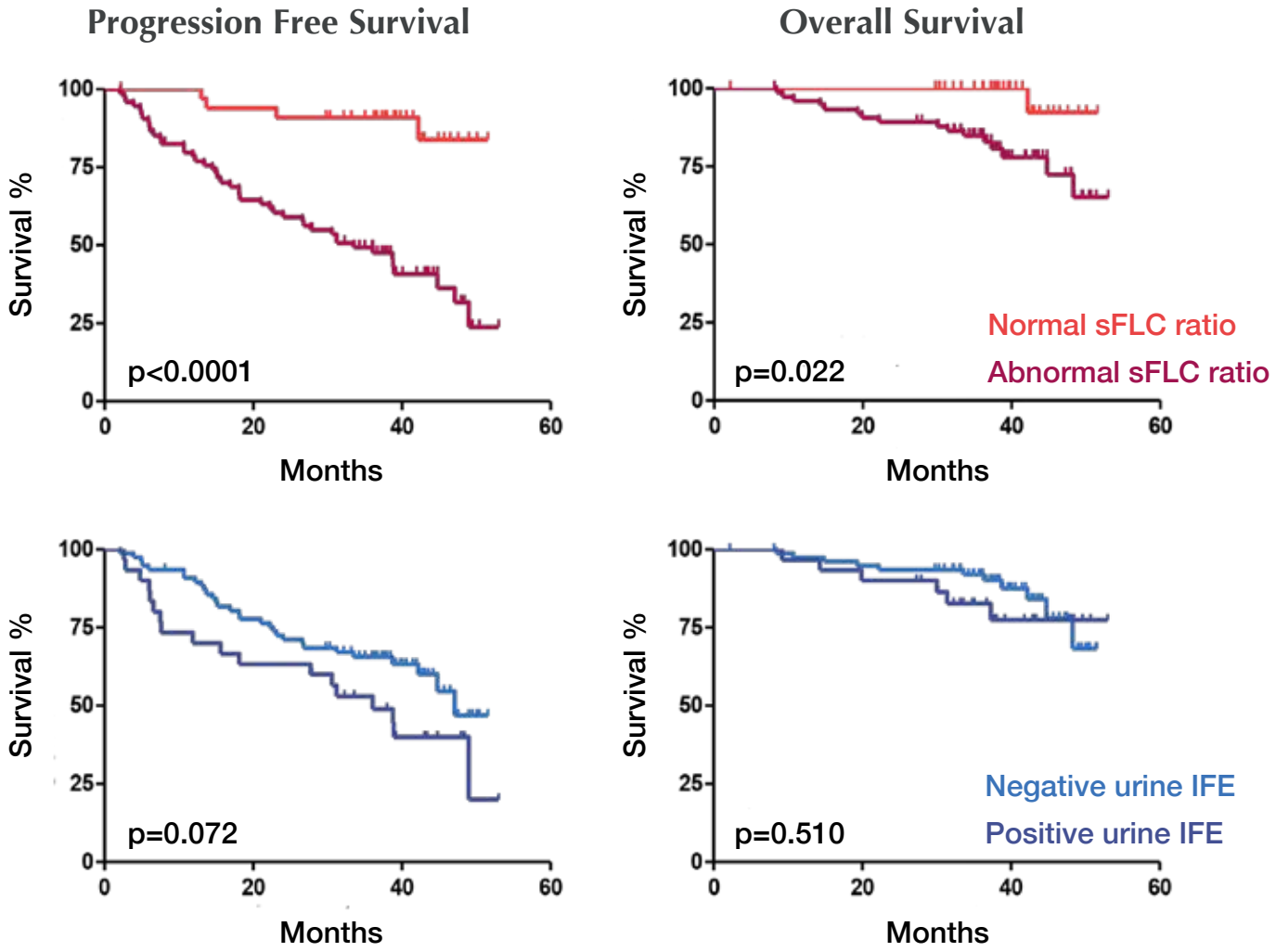
dFLC = involved Free Light Chain - uninvolved Free Light Chain UPE = Urine Protein Electrophoresis uIFE = urine Immunofixation Electrophoresis
ASCT = Autologous Stem Cell Transplant uBJP = urine Bence Jones Protein sIFE = Serum Immunofixation Electrophoresis FLC = Free Light Chain

Greater biological relevance of sFLC analysis over urine for LCMM

The increased sensitivity of sFLC analysis when monitoring Light Chain Multiple Myeloma patients translates into valuable prognostic information.

Post therapy, patients with an abnormal sFLC ratio had a worse outcome.

uIFE provided no prognostic information.[16]



"…serum FLC analysis is the method of choice for response evaluation in LCMM patients…" [16]

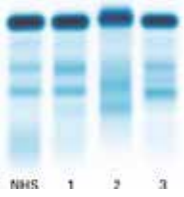
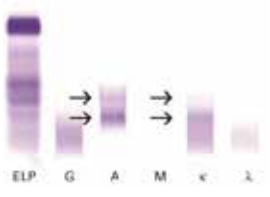
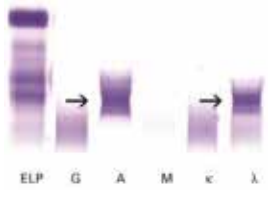
sFLC = Serum Free Light Chain uIFE = Urine Immunofixation Electrophoresis LCMM = Light Chain Multiple Myeloma

Hevylite assays overcome the difficult measurement of IgA monoclonal proteins

IgA monoclonal proteins are often difficult to quantify, and therefore difficult to monitor, by SPE.

This can be due to small bands, broadly migrating bands, or co-migration with other serum proteins.

Accurate numerical values by **Hevylite** assays make it easier to monitor IgA Multiple Myeloma patients.

SPE for patients 1-3	IFE for Patient 1	IFE for Patient 2	IFE for Patient 3
			
	IFE is used here to confirm why SPE is not quantifiable in these 3 patients:		
	Patient 1	**Patient 2**	**Patient 3**
	The IgAκ band is too small to quantify by SPE	The broadly migrating IgAκ is hard to separate from the polyclonal background on SPE	IgAλ co-migrates with other serum proteins on SPE
Hevylite ratio	37.17 (Abnormal)	44.39 (Abnormal)	0.17 (Abnormal)
dHLC	3.58	16.62	4.44

Arrows indicate monoclonal immunoglobulin on IFE

All 3 patients had abnormal **Hevylite** assay ratios, indicating monoclonality. When the **Hevylite** assays ratio is abnormal, these patients can also be monitored using dHLC.

*"The **Hevylite** assay...can overcome limitations associated with monitoring beta-migrating monoclonal IgA by electrophoresis"* [17]

Use Hevylite assays when electrophoresis is inaccurate

SPE = Serum Protein Electrophoresis IFE = Immunofixation Electrophoresis dHLC = involved Heavy Light Chain - uninvolved Heavy Light Chain (see page 23)
NHS = normal human serum

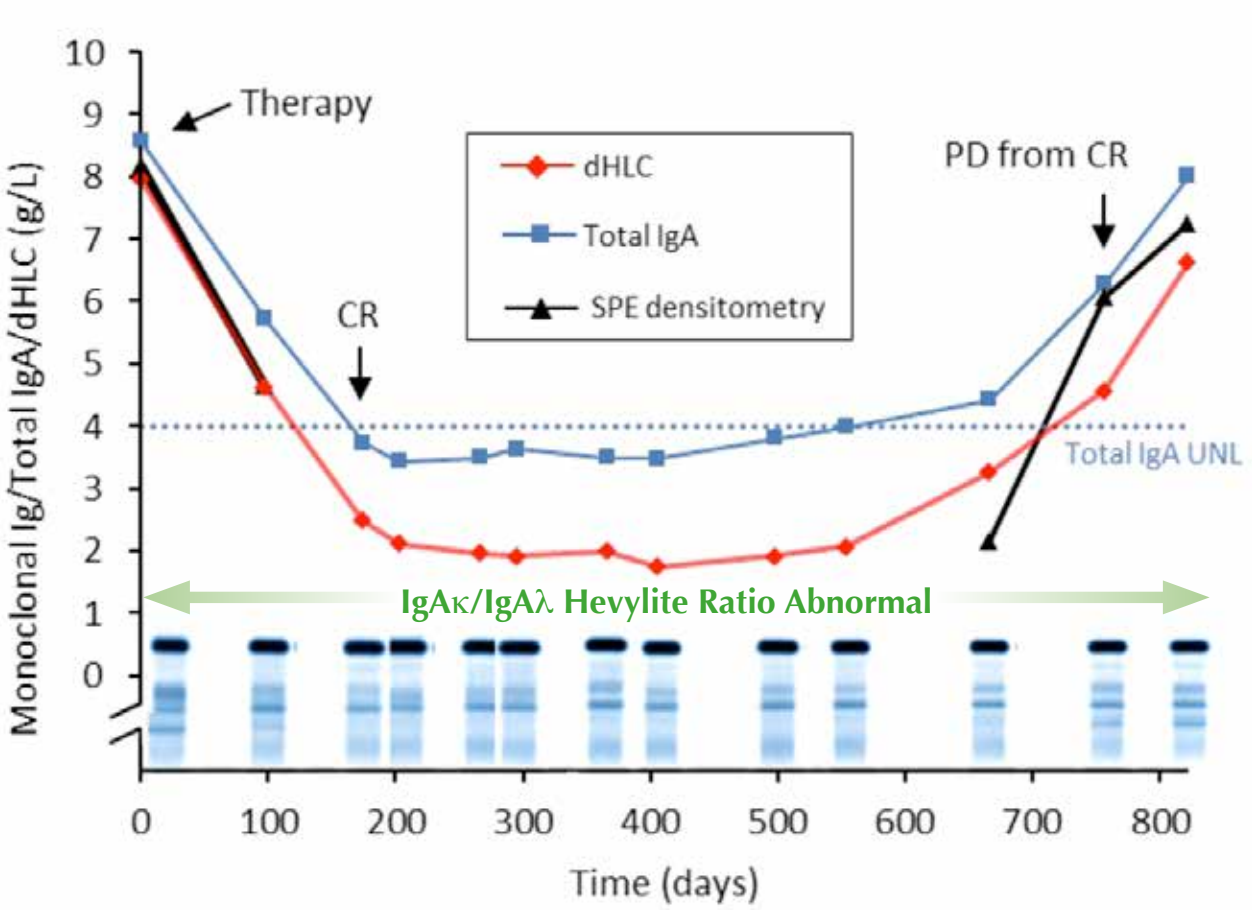
Accurately monitor low levels of monoclonal protein <10g/L

Oligosecretory disease - Monitor with Hevylite and Freelite

Freelite assays are recommended by IMWG guidelines for monitoring Oligosecretory Multiple Myeloma due to their high sensitivity compared to traditional techniques.[3, 18]

The IMWG consensus criteria for response and MRD assessment in multiple myeloma acknowledge the value of using **Hevylite** assays in such cases.

> *"The **Hevylite** assay is useful in patients with oligo-secretory disease..."* [17]



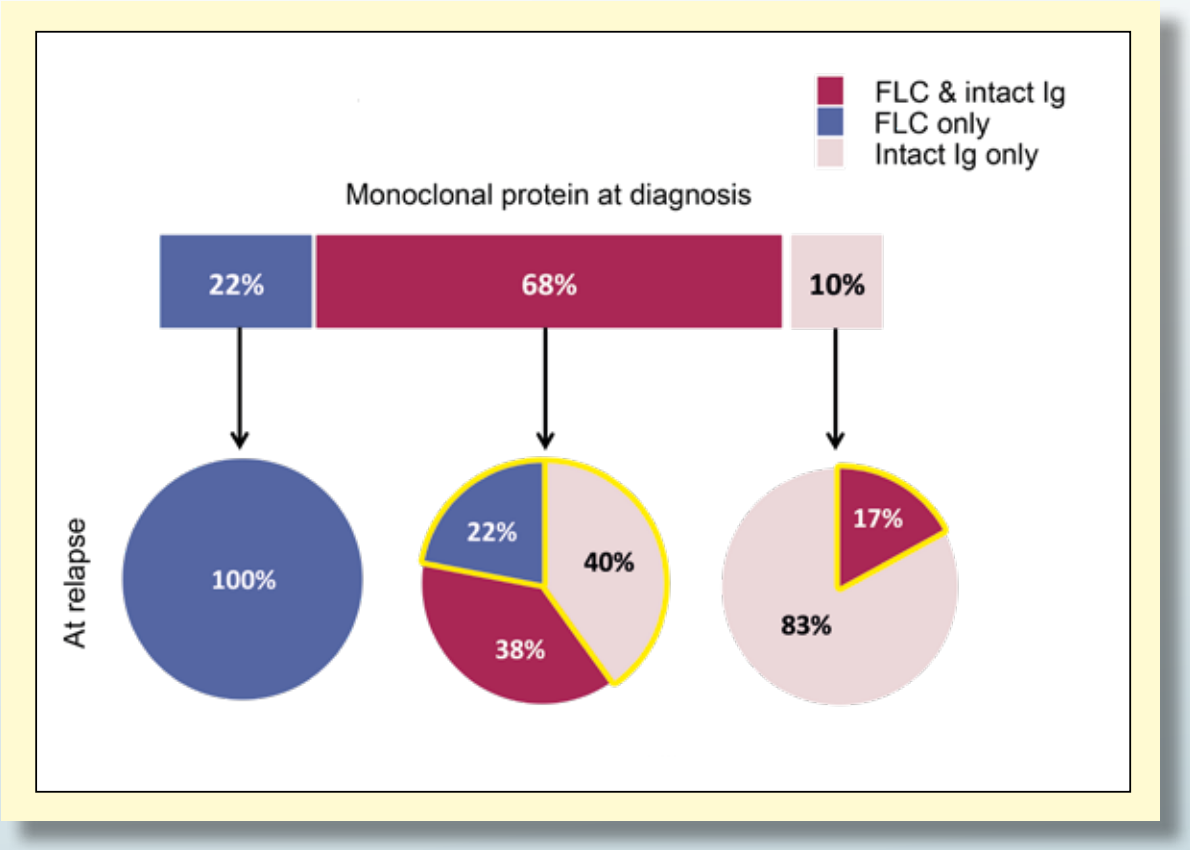
This IgAκ myeloma patient presented with very low levels of monoclonal protein. At Complete Response, SPE and total IgA are normal until disease progression (PD) but the patient's monoclonal protein can be monitored throughout using **Hevylite** assays. The **Hevylite** assays ratio does not normalise, indicating residual disease

Use Hevylite assays when electrophoresis is insensitive

IMWG = International Myeloma Working Group SPE = Serum Protein Electrophoresis Ig = Immunoglobulin CR = Complete Response PD = Progressive Disease
dHLC = involved Heavy + Light Chain isotype - uninvolved Heavy + Light Chain isotype UNL = Upper normal limit MRD = Minimal Residual Disease

Clonal Diversity at relapse

Serum FLCs and intact immunoglobulins are independent tumour markers.



Monoclonal protein type detected at relapse and progression can be different to those seen at diagnosis.[19]

1. Free light chain only patients showed no change
2. 62% of patients with both intact immunoglobulins and FLCs changed their monoclonal protein type
3. 17% of patients with only intact immunoglobulins changed their monoclonal protein type

Overall, **44%** of patients changed their monoclonal protein type at relapse.

Used together, Freelite and Hevylite assays can identify clonal change at relapse

FLCs = Free Light Chains Ig = Immunoglobulin

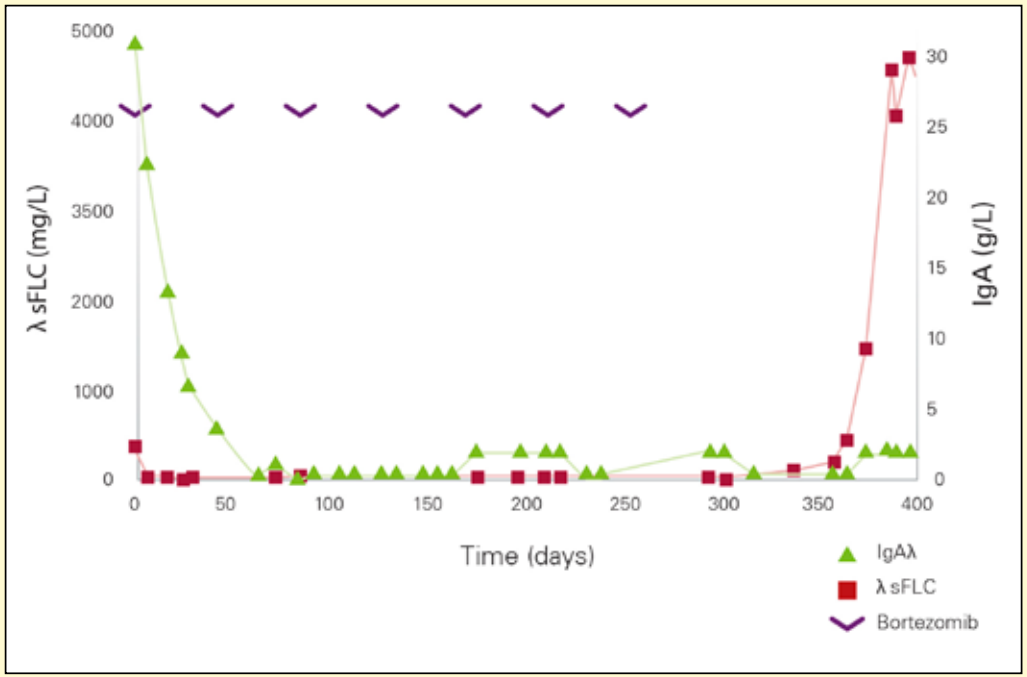
Detect Light Chain Escape to improve patient outcome

For some IIMM patients, relapse is accompanied by a marked rise in monoclonal sFLC with no associated increase in intact immunoglobulin concentrations.

This phenomenon is known as light chain escape or Bence Jones escape.

Patients who relapse with any light chain involvement have poorer prognosis than those relapsing with intact immunoglobulins only.[20]

10% of IIMM patients (20% of IgA IIMM) relapse with FLC only.



Courtesy of Christie Hospital, Manchester, UK.

This Intact Immunoglobulin MM patient was monitored following bortezomib treatment (▼). Both IgAλ and λ serum FLC levels decrease in response to treatment and remain stable for many months.

Subsequent relapse with LCE was only detected by **Freelite** assays.

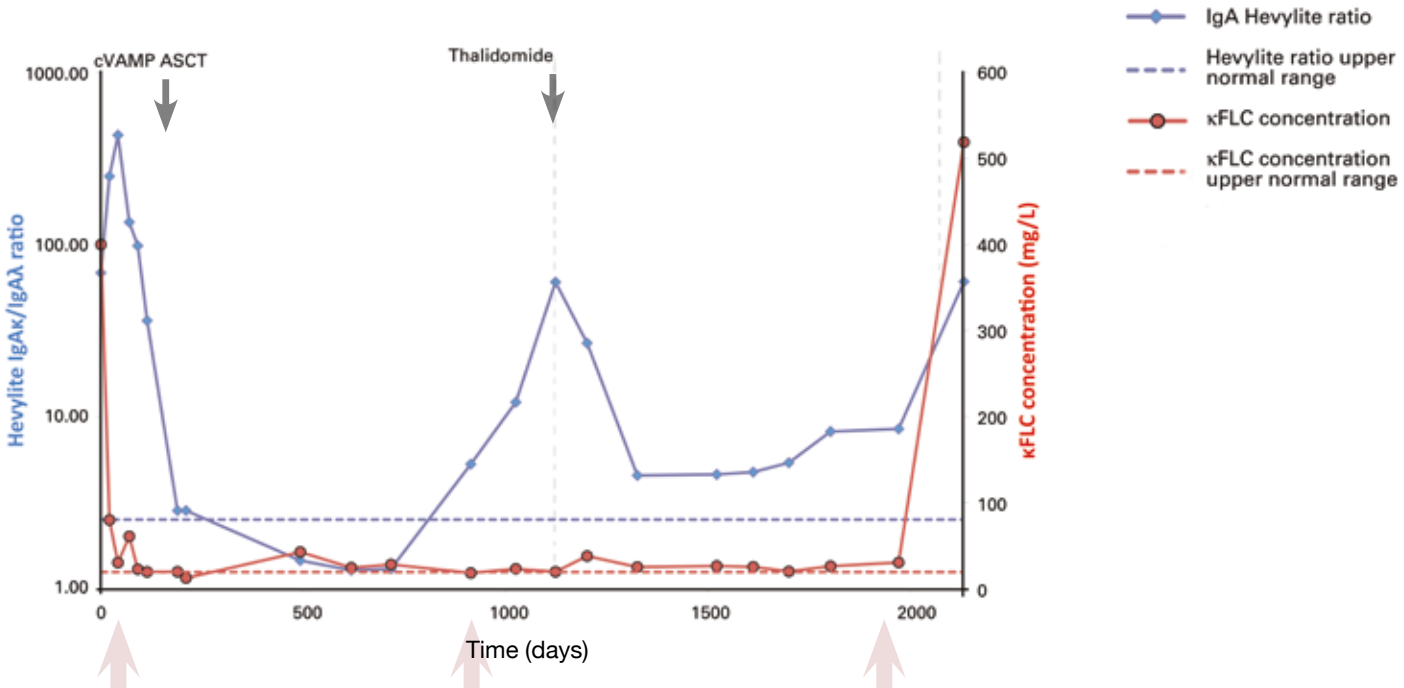
Monitor with Freelite assays to ensure Light Chain Escape is not missed[20]

MM = Multiple Myeloma LCE = Light Chain Escape FLC = Free Light Chain sFLC = serum Free Light Chain IIMM = Intact Immunoglobulin Multiple Myeloma

Use Freelite and Hevylite assays together to capture clonal change

Freelite and **Hevylite** assays measure two independent biomarkers in Multiple Myeloma.

- **Freelite** assays measure kappa(κ) and lambda(λ) free light chains (mg/L)
- **Hevylite** assays measure intact monoclonal immunoglobulins (g/L)



The patient presented with abnormal **Hevylite** and **Freelite** assay ratios. Following treatment both the **Hevylite** assays ratio and κFLC concentrations normalise.

By day 900 the patient relapsed with an increase in IgA **Hevylite** assays ratio but little change in the κFLC levels.

After further treatment the **Hevylite** assays ratio did not normalise. Further relapse was seen at around 2000 days with both an increase in the **Hevylite** ratio and κFLC concentration.

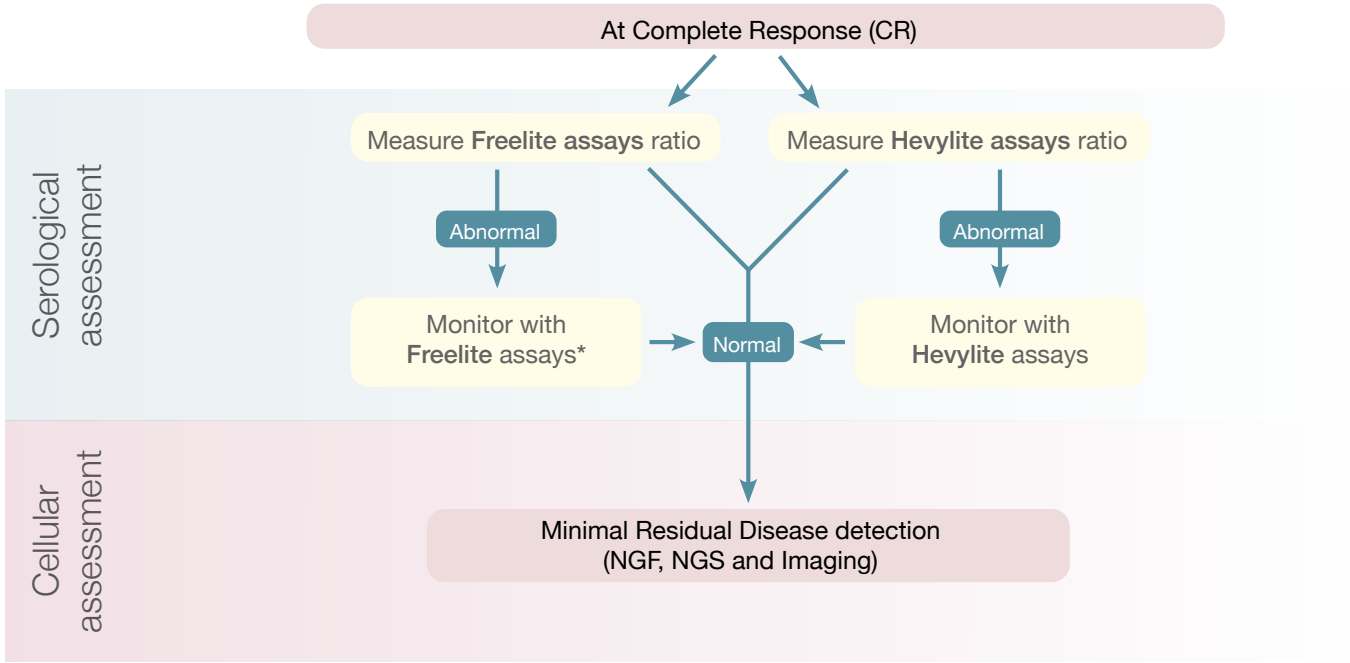
When used together, **Freelite** assays and **Hevylite** assays provide more accurate information on multiple myeloma disease course, as highlighted by this case example of IgA kappa Multiple Myeloma.

Freelite and **Hevylite** assays are both quantitative and easy to use, combining accurate results with high sensitivity, enabling rapid identification of clonal change at relapse.

κFLC = Kappa Free Light Chain cVAMP = Cyclophosphamide Vincristine Doxorubicin Methylprednisolone ASCT = Autologous Stem Cell Transplant

Residual Disease

Use Freelite and Hevylite assays together as gateway tests to MRD assessment



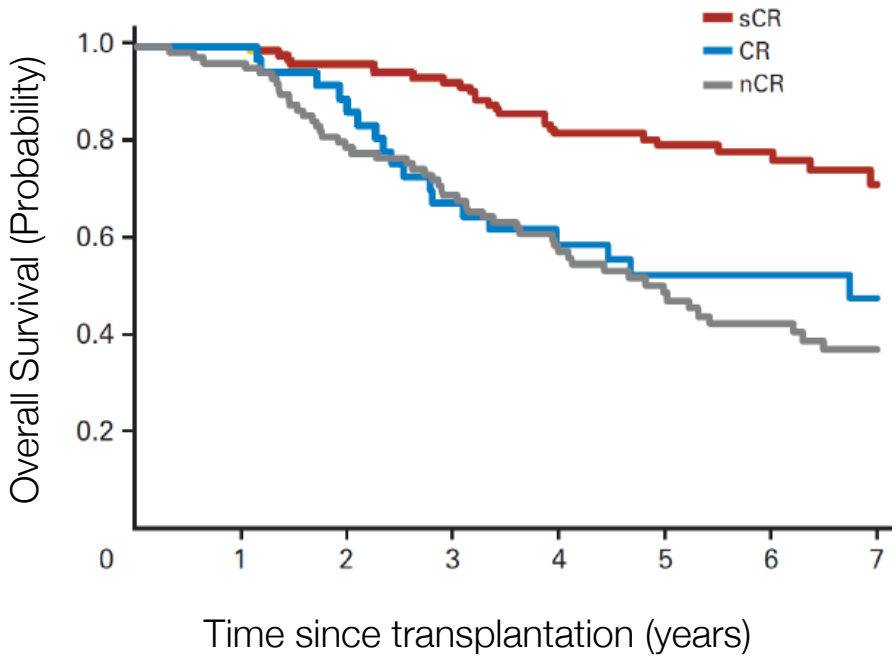
* Normal Freelite ratio to help define Stringent Complete Response

Negative IMWG MRD criteria **+** Normal **Hevylite** assays ratio **=** *"Composite endpoint reflecting the eradication of tumour cells from all compartments and recovery of the normal plasma-cell population to the currently available level of detection"* [17]

To provide additional sensitivity use Freelite and Hevylite assays together

NGF = Next Generation Flow Cytometry NGS = Next Generation Sequencing MRD = Minimal Residual Disease IMWG = International Myeloma Working Group

Freelite assays are essential for assessing sCR in all myeloma patients



Complete Response

- Negative serum/ urine IFE
- BM plasma cells <5%

Stringent Complete Response

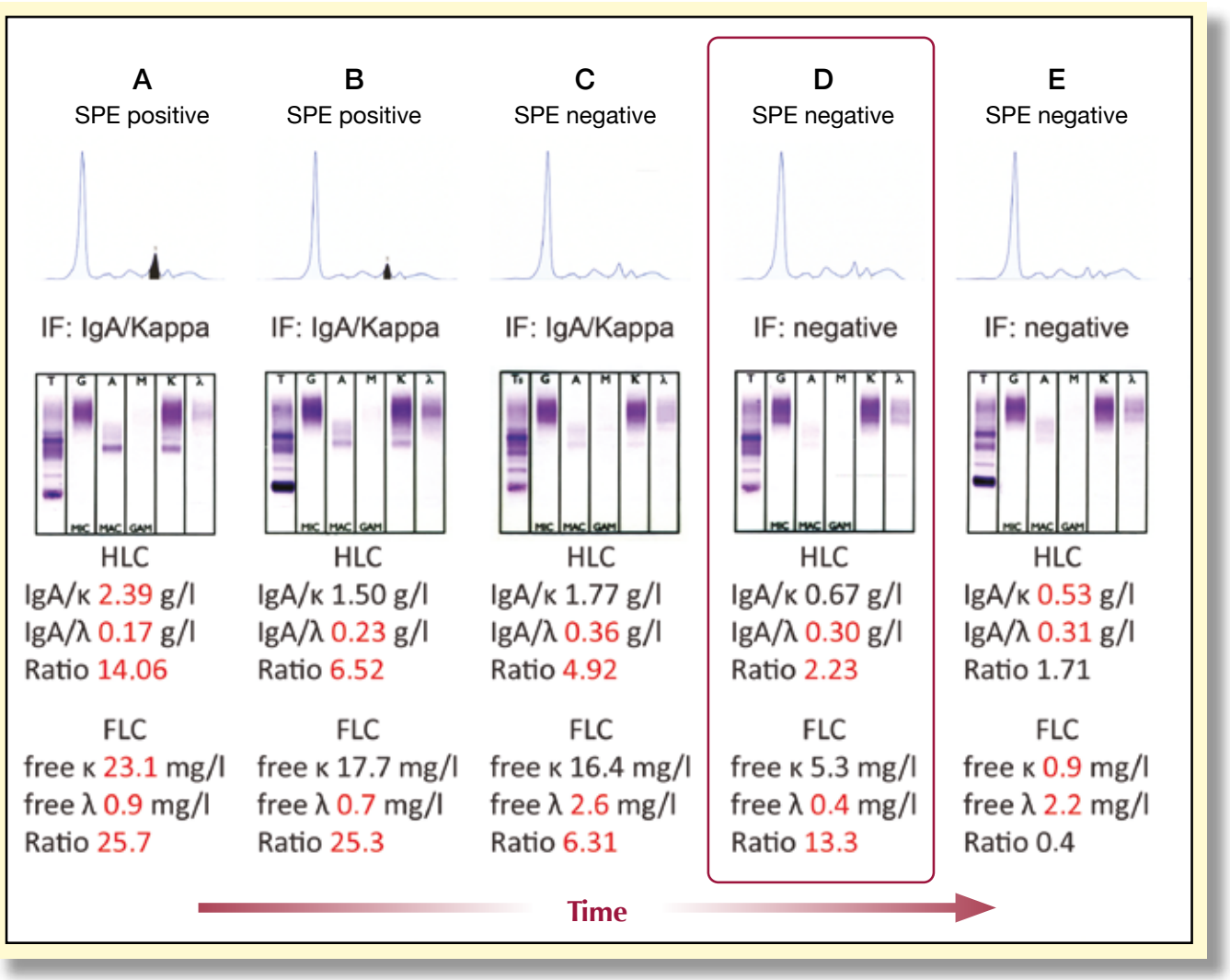
- Negative serum/ urine IFE
- Absence of clonal cells in BM
- **Normal sFLC ratio**

Patients who managed to reach sCR after ASCT transplantation had significantly improved overall survival. Those who could sustain a sCR for at least 6 months had the best overall survival.[21]

Patients who achieved a sCR had significantly longer survival than those who achieved a CR

sCR = stringent Complete Response CR = Complete Response IFE = Immunofixation Electrophoresis nCR = Near Complete Response
sFLC = Serum Free Light Chains BM = Bone Marrow ASCT = Autologous Stem Cell Transplant

Use Hevylite assays to capture more residual disease



The increased sensitivity of **Hevylite** assays can indicate the presence of residual disease in patients classified as being in Complete Response by other methods (D).[22]

The abnormal **Hevylite** assays ratio of this patient in B-D is produced by immunosuppression of the uninvolved immunoglobulin (IgAλ) rather than an increase in the involved IgAκ, highlighting the unique information provided by **Hevylite** assays.

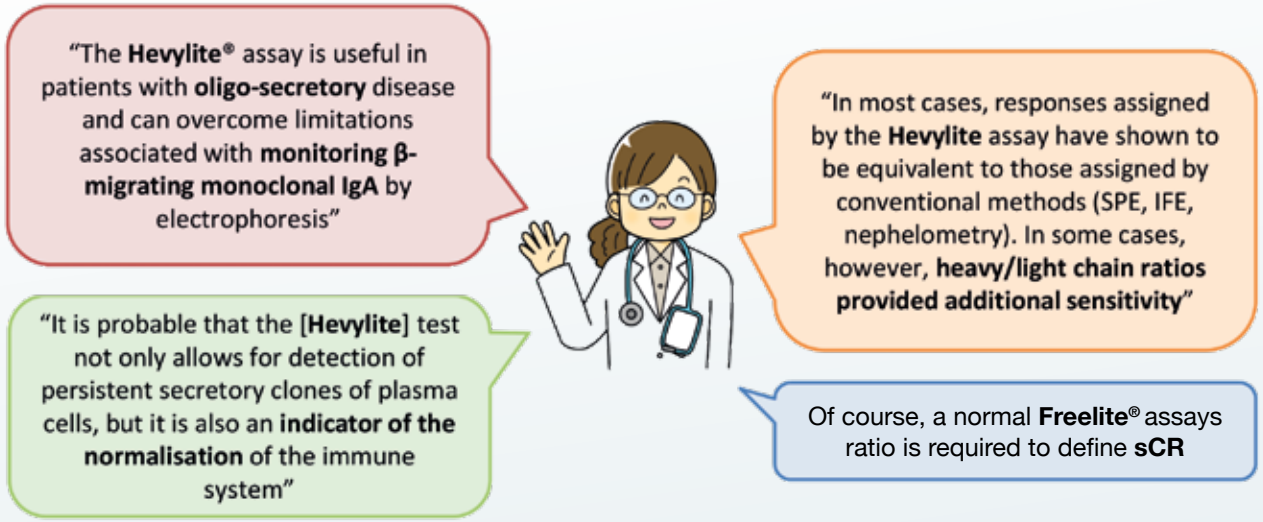
Red = abnormal Hevylite/Freelite assays result

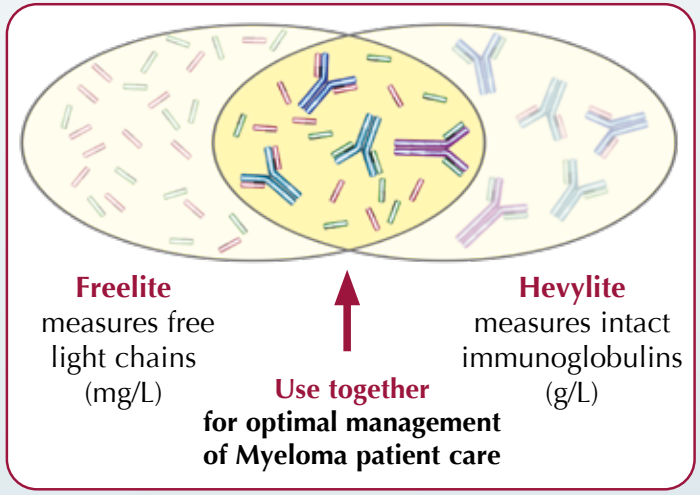
*"It is probable that the [**Hevylite** assay] test not only allows for the detection of persistent secretory clones of plasma cells, but it is also an indicator of the normalisation of the immune system."* [17]

More information for better patient care decisions

IF = Immunofixation Electrophoresis SPE = Serum Protein Electrophoresis HLC = Heavy + Light Chain Isotypes FLC = Free Light Chain

International Myeloma Working Group (IMWG) Consensus Criteria for Response and MRD Assessment in Multiple Myeloma[17]





Freelite and Hevylite assays measure two independent biomarkers in Myeloma

MRD = Minimal Residual Disease SPE = Serum Protein Electrophoresis IFE = Immunofixation Electrophoresis sCR = Stringent Complete Response

Key Terminology

Freelite assays

Term	Definition	Description	Example in κ light chain MM
FLC	Free Light Chain		
iFLC	Involved FLC	FLC type produced by the tumour	κ
uFLC	Uninvolved FLC	FLC type that is the alternate light chain type to the iFLC	λ
κ/λ sFLC ratio	κ/λ	Ratio of the concentration of κ to λ sFLCs (indicates clonality)	κ/λ
dFLC	iFLC – uFLC	Difference in concentration between iFLC and uFLC	κ – λ
iFLC/uFLC ratio		Ratio of the concentration of iFLC to uFLC (can be κ/λ or λ/κ)	κ/λ

Hevylite assays

Term	Definition	Description	Example in an IgAκ MM patient
HLC	Heavy + light chain isotypes	Measures heavy/light chain combination, not separately	
iHLC	Involved HLC	HLC isotype produced by the tumour	IgAκ
uHLC	Uninvolved HLC	The same heavy chain isotype but alternate light chain type to the iHLC	IgAλ
HLC ratio	e.g. IgAκ/IgAλ	For a particular immunoglobulin isotype, a ratio of the concentration of Hevylite κ to λ (indicates clonality)	IgAκ/IgAλ
dHLC	iHLC – uHLC	For a particular immunoglobulin isotype, the difference in concentration between the iHLC and uHLC	IgAκ-IgAλ
Hevylite pair suppression	When the concentration of the uHLC is below the normal reference interval	The HLC ratio must be abnormal	Suppression of IgAλ

MM = Multiple Myeloma

Reference ranges

Freelite assays

Normal adult serum	95 percentile range
κ FLC	3.30 - 19.40 (mg/L)
λ FLC	5.71 - 26.30 (mg/L)
κ / λ FLC ratio	**100 percentile range**
	0.26 - 1.65

An abnormal k/l FLC ratio is a highly sensitive indicator of monoclonal k or l FLC in serum. A study showed that patients with renal impairment had increased levels of FLC in serum and proposed an extended **Freelite** ratio reference range k/l FLC ratio: 0.37-3.1 for these patients.[23]

Renal reference range	100 percentile range
κ / λ FLC ratio	0.37 - 3.1

The renal reference range improves specificity whilst maintaining diagnostic sensitivity in patients with renal impairment.
Values outside of this range are consistent with the presence of monoclonal sFLC's in these patients.

Hevylite assays

Normal adult serum	95 percentile range for Optilite®
IgG Kappa	4.03 - 9.78 (g/L)
IgG Lambda	1.97 - 5.71 (g/L)
IgGκ/IgGλ Ratio	0.98 - 2.75
IgA Kappa	0.588 - 2.984 (g/L)
IgA Lambda	0.432 - 2.035 (g/L)
IgAκ/IgAλ Ratio	0.911 - 2.416
IgM Kappa	0.19 - 1.63 (g/L)
IgM Lambda	0.12 - 1.01 (g/L)
IgMκ/IgMλ Ratio	1.18 - 2.74

FLC = Free Light Chain sFLC = serum Free Light Chain

Key Guidelines

Year	Guidelines	Author & Publication Information
2016	International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma.	Kumar, *et al*. *Lancet Oncology* 2016; 17:e328-346
2016	National Institute for Health and Care Excellence (NICE). Myeloma: diagnosis and management.	NICE publication (UK)
2016	National Comprehensive Cancer Network (NCCN). Clinical practice Guidelines in Oncology - Multiple Myeloma	Anderson KC, *et al*; NCCN publication
2014	International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma.	Rajkumar SV, *et al*. *Lancet Oncology* 2014; 15:e538-e548
2014	International Myeloma Working Group recommendations for global myeloma care.	Ludwig H, *et al*. *Leukemia* 2014; 28:981-992
2012	New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes.	Palladini, *et al*. *J Clin Onc* 2012; 30:4541-4549
2011	Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1.	Rajkumar SV, *et al*. *Blood* 2011; 117:4691-4695
2010	Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management.	Kyle RA, *et al*. *Leukemia* 2010; 24:1121-1127
2009	International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders.	Dispenzieri A, *et al*. *Leukemia* 2009; 23:215-224
2006	International uniform response criteria for multiple myeloma.	Durie BGM, *et al*. *Leukemia* 2006; 20:1467-1473

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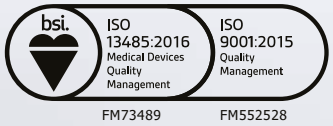

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