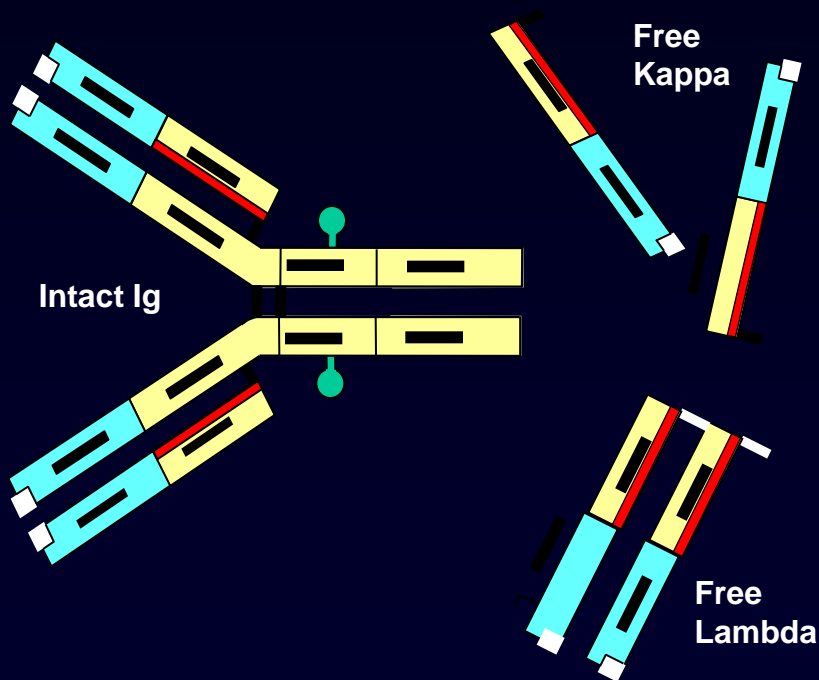


Serum Free Light Chain Assays in the Diagnosis and Monitoring of Multiple Myeloma and Other Monoclonal Gammopathies

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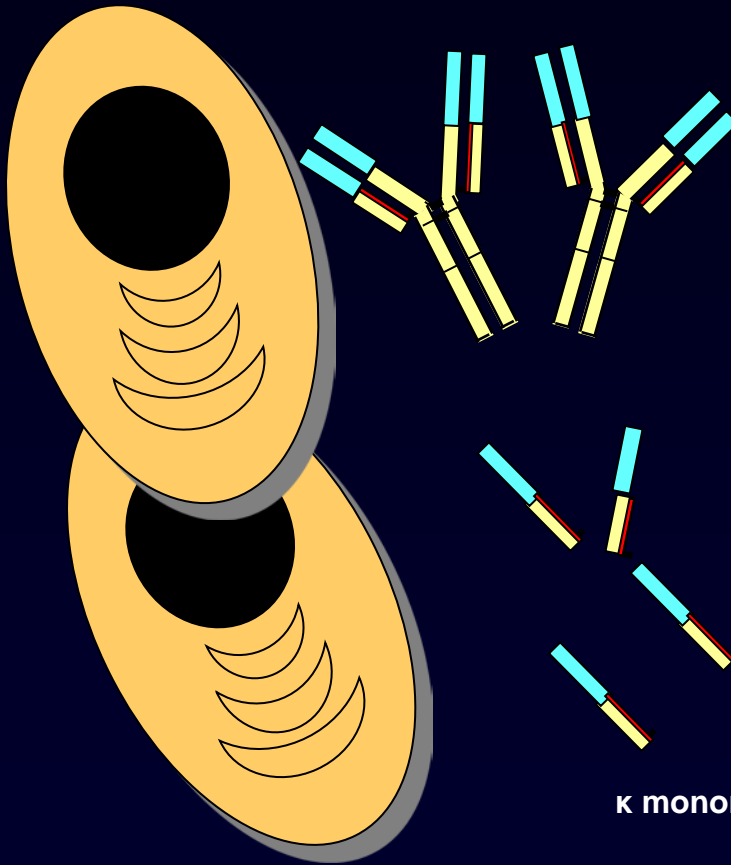
Serum Free Light Chain Assays: Highly Sensitive Fully Automated Blood Tests for the Detection and Monitoring of Multiple Myeloma and Other Monoclonal Gammopathies



Normal Ranges

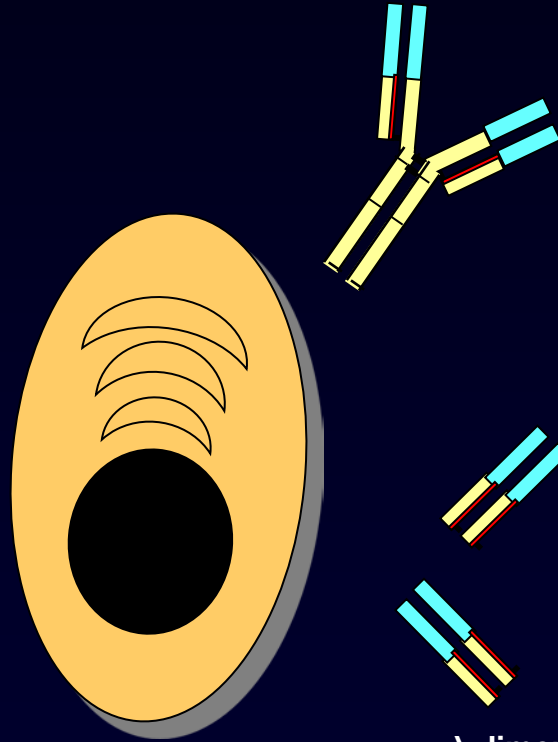
- Serum Free Kappa 3.3 – 19.6 mg/L
- Serum Free Lambda 5.6 – 26.3 mg/L
- Kappa/Lambda ratio: 0.26 – 1.65

Kappa-Producing Plasma Cells Outnumber Lambda-Producing Plasma Cells by $\geq 2:1$



κ monomer 25 kDa

Kappa

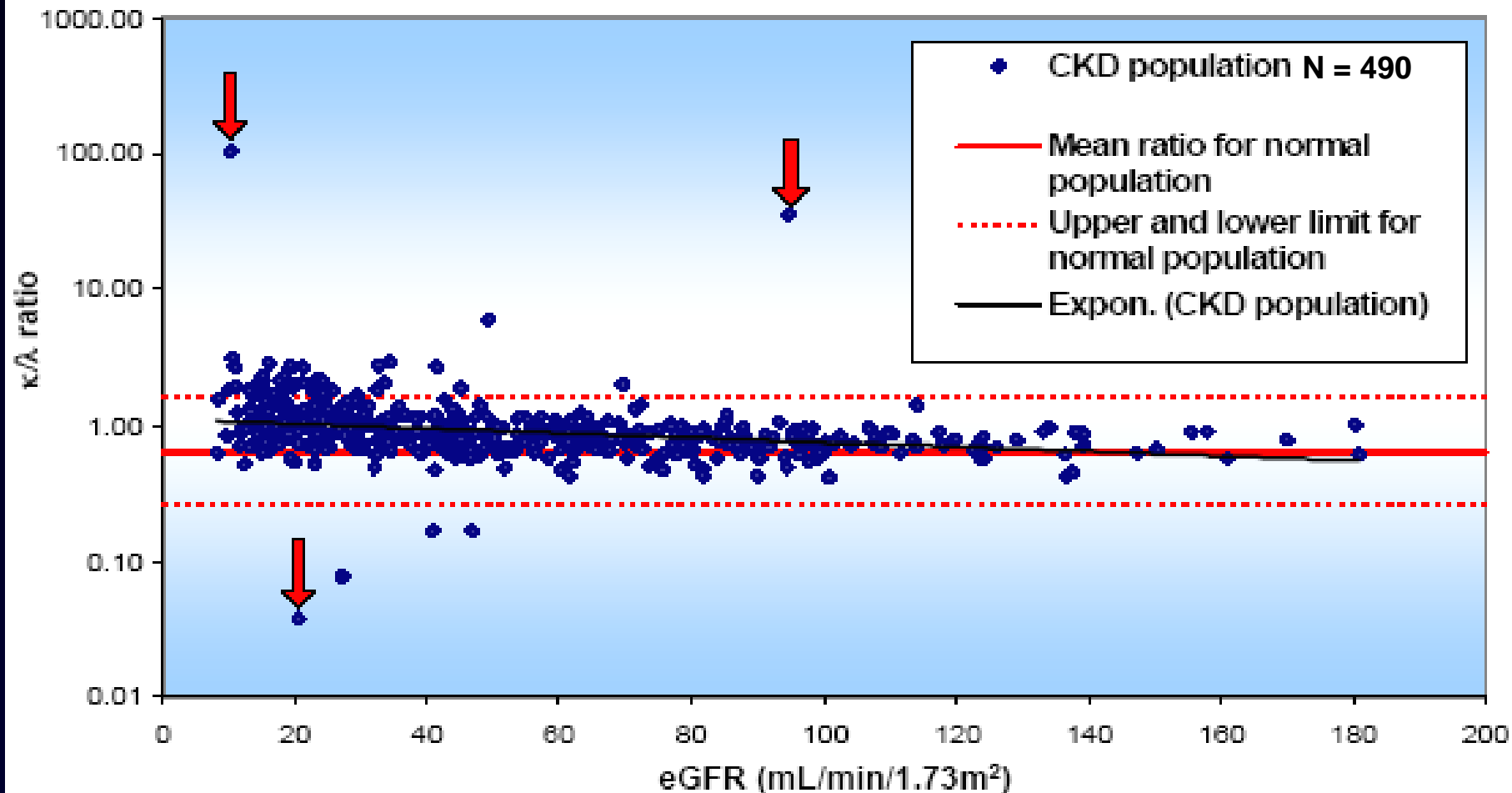


λ dimer 50 kDa

Lambda

Serum Free Light Chain Results in CKD

eGFR V κ/λ ratio in a CKD population



Polyclonal Gammopathy

- N = 25
- Hypergammaglobulinemia (18–39 g/L) on SPEP but no monoclonal protein by IFE

	Median	Range	Abnormal, %
Kappa, mg/L	19.6	4.3 – 273	52
Lambda, mg/L	28.8	8.5–307	58
κ/λ ratio	0.55	0.38–1.18	0

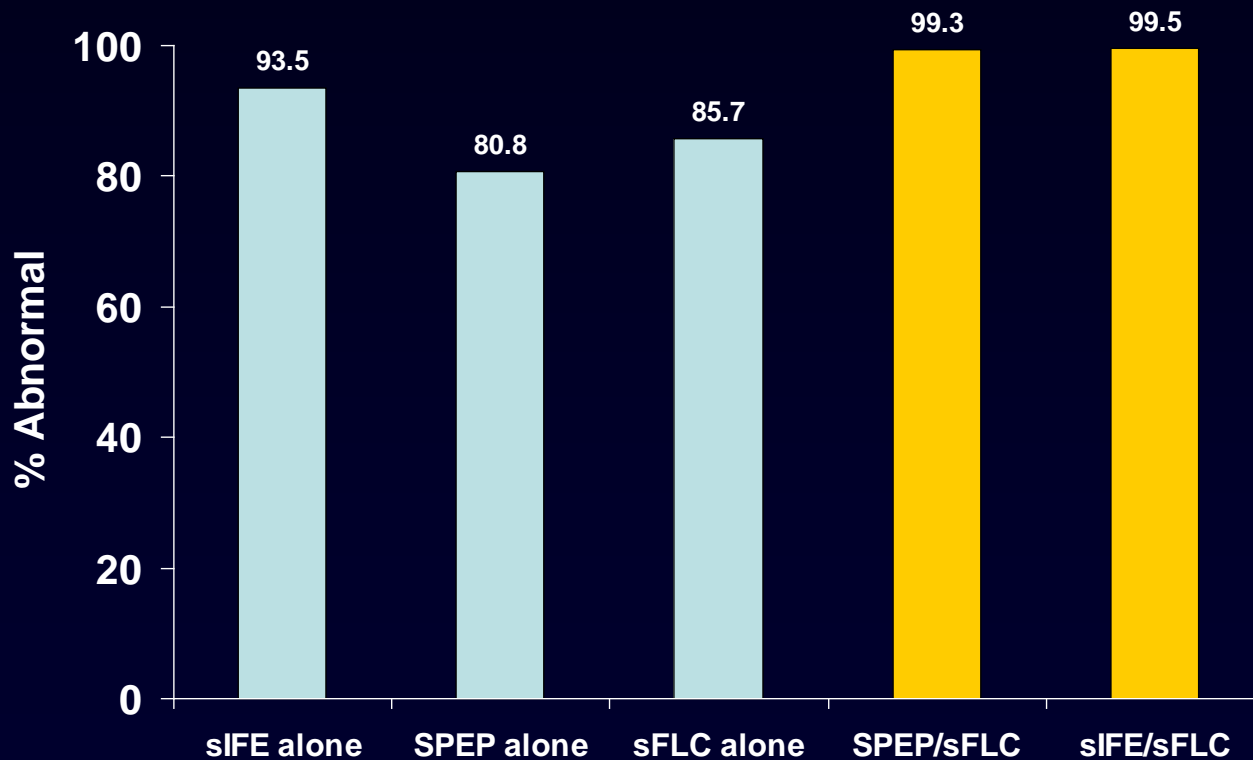
Improved Sensitivity When Added to SPEP

	Myeloma	AL Amyloidosis	Light Chain Multiple Myeloma	Non Secretory Myeloma
	% of Paraproteins Detected			
SPEP alone	90%	50%	50%	0%
SPEP and serum free light chain assays	99%	98%	99%	82%

Bradwell et al. *Lancet*. 2003; 361:489–91.
Lachmann et al. *Br J Haematol*. 2003;122:78-84.
Drayson et al. *Blood*. 2001;97:2900-2.

Optimal Screening Panel to Eliminate Urine Testing - Mayo Clinic

N = 428 abnormal urine IFE

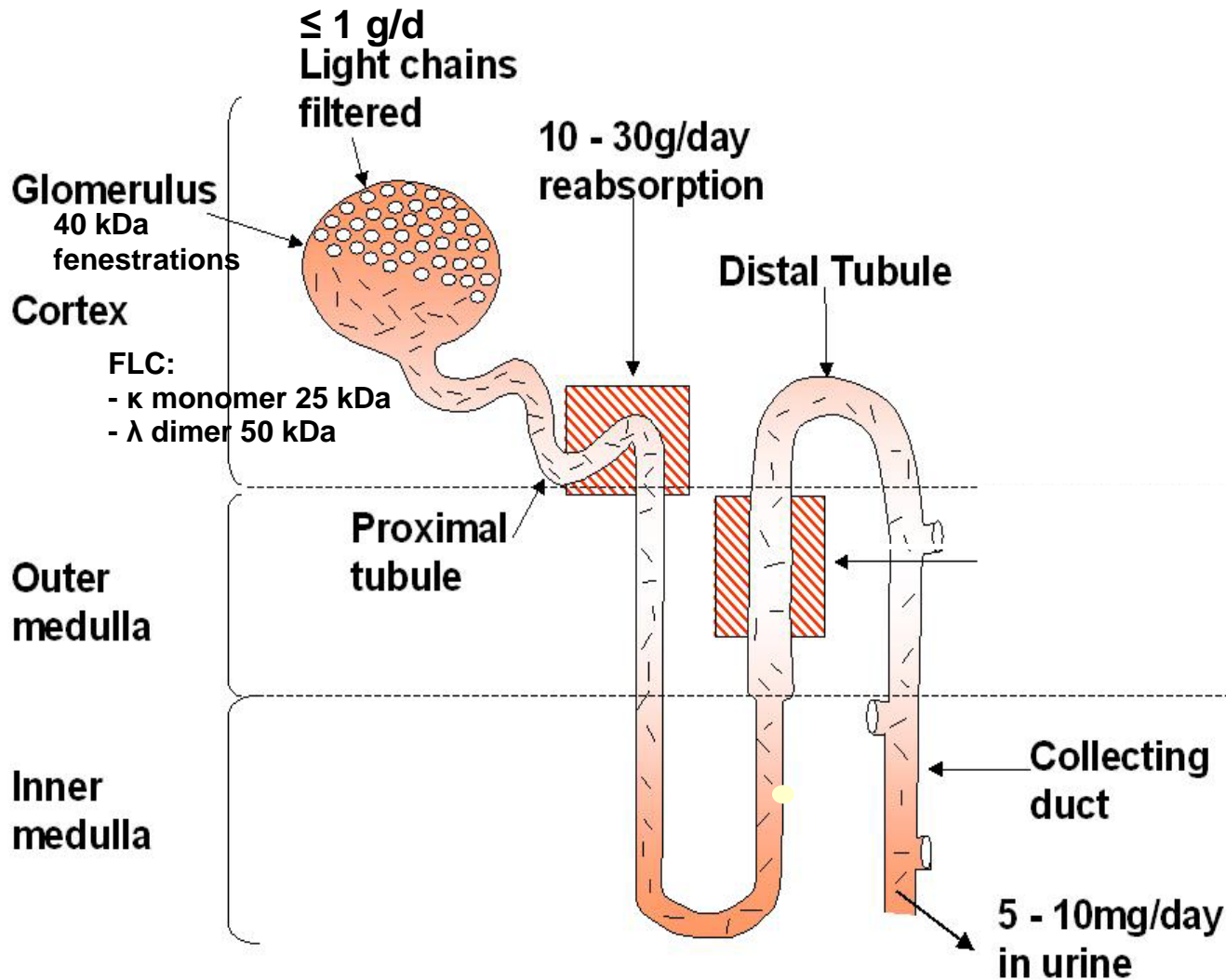


SPEP/IFE negative but sFLC abnormal in:

- 19 AL amyloidosis**
- 3 solitary plasmacytoma**
- 2 myeloma**
- 1 smoldering myeloma**

Serum More Sensitive Than Urine

κ Filtered 3x Faster Than λ



sFLC vs Urine IFE in Multiple Myeloma

	Serum [kappa FLC]	Serum [lambda FLC]
IFE-negative urine	Median 40 mg/L Range 6–710 mg/L n = 48	Median 44 mg/L Range 3–561 mg/L n = 70

- Serum free light chain levels were more sensitive than urine IFE for detection of abnormalities

International Guidelines for Diagnosis of Multiple Myeloma

1. M-protein in the serum and/or urine by SPEP, 24-h UPEP, IFE, or **abnormal serum free light chain ratio***
2. $\geq 10\%$ monoclonal plasma cells in the bone marrow and/or presence of a biopsy-proven plasmacytoma
3. Myeloma-related organ dysfunction (CRAB)
 - Hypercalcemia
 - Renal insufficiency
 - Anemia
 - Bone lesions (osteolytic lesions) or osteoporosis

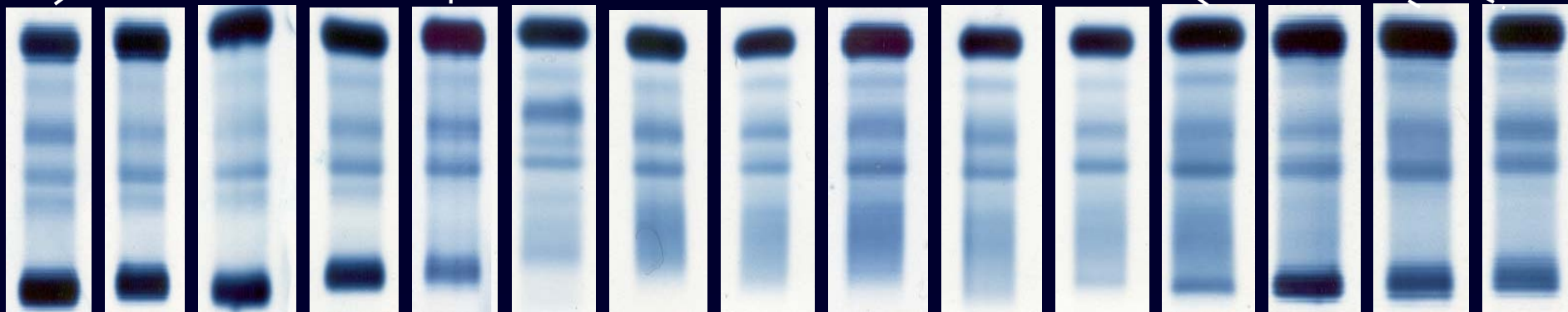
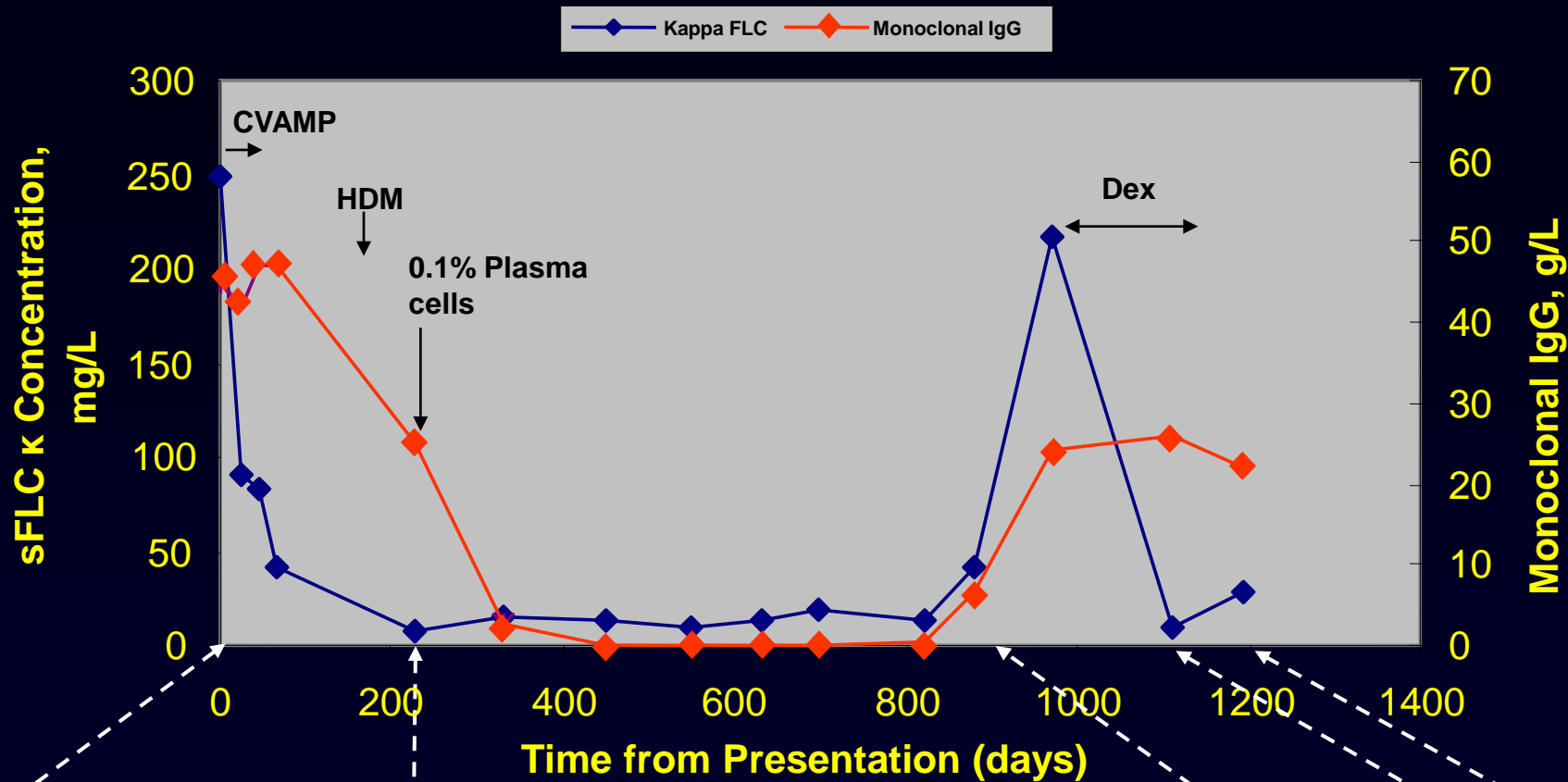
*If none identified, need $\geq 30\%$ PC in BM or bx-proven plasmacytoma

Monitoring Response to Tx

Immunoglobulin Half-Life

<u>Protein</u>	<u>Half Life</u>
IgG	20–25 days
IgA	6 days
IgM	6–8 days
Free Kappa	2–4 hours
Free Lambda	3–6 hours

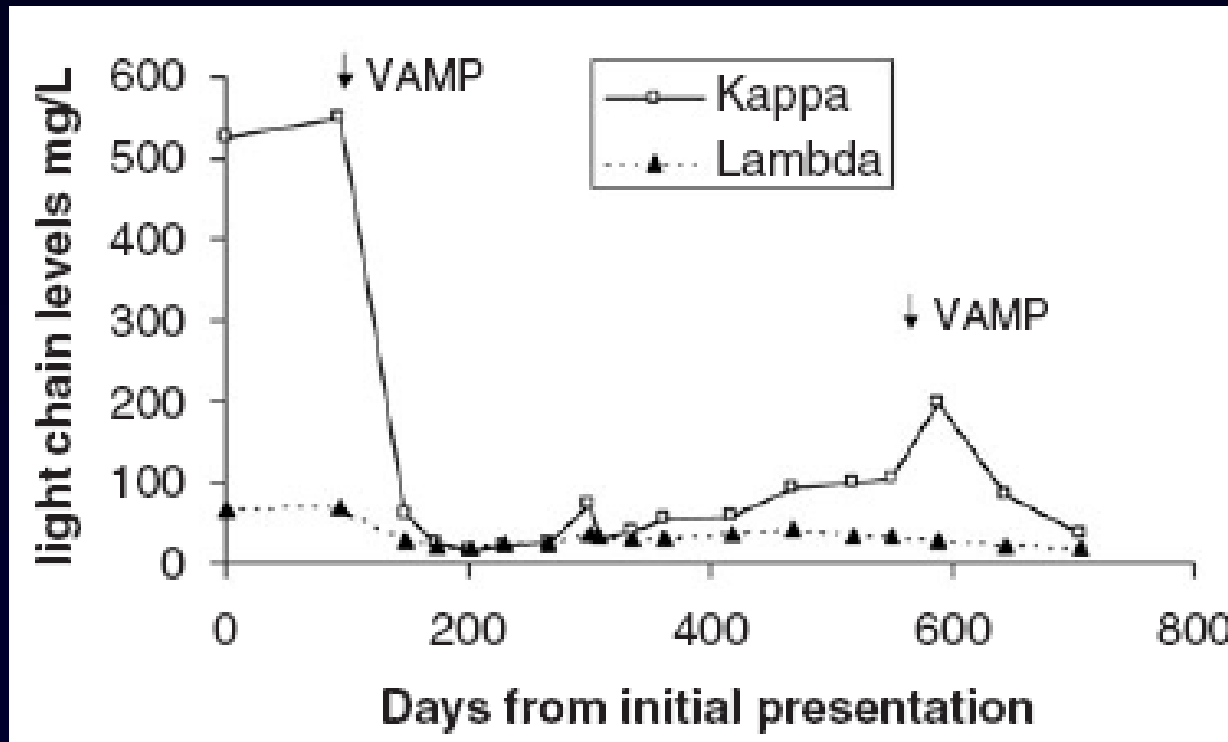
IgG κ Multiple Myeloma



SPEP Gels

LCDD Case Study

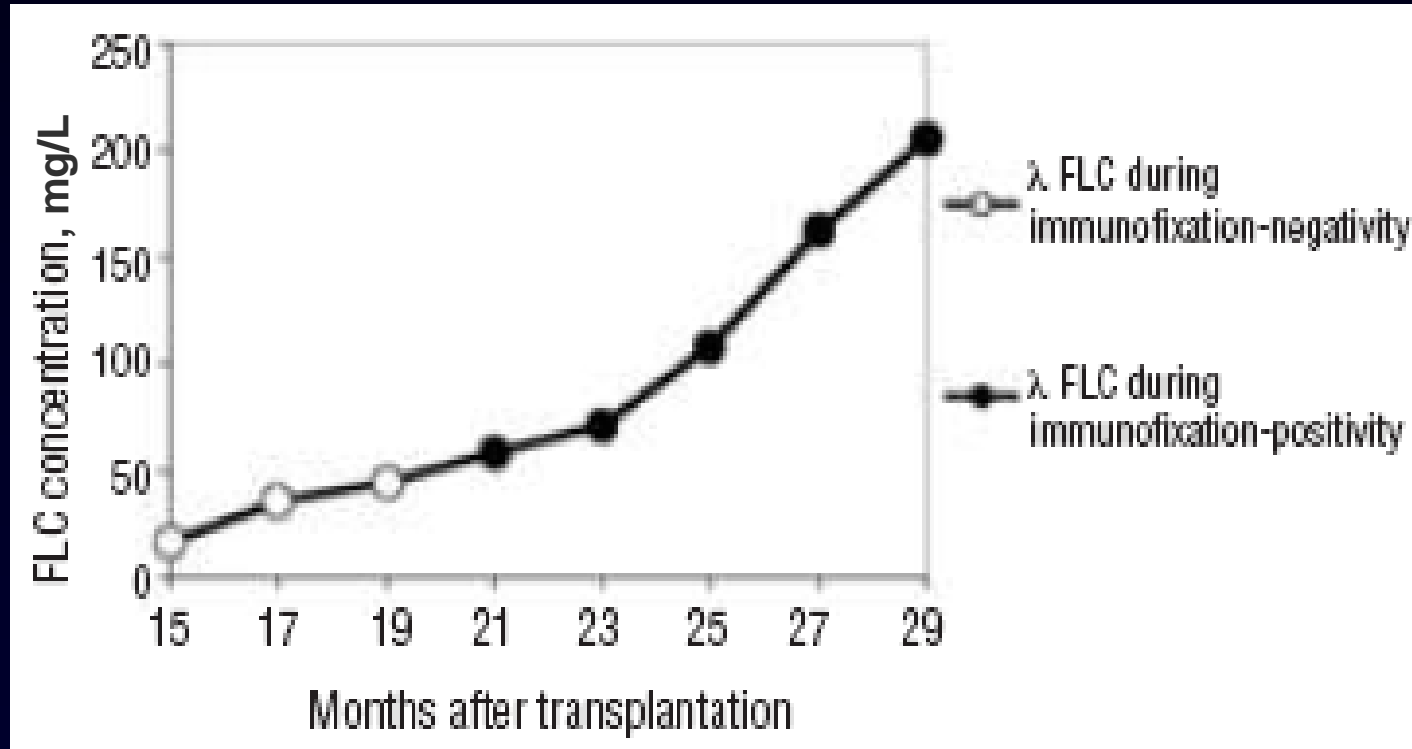
- 59-year-old man with nephrotic syndrome
- Renal bx: nodular GS; EM+ for granular electron-dense material along tubular BM
- Serum free light chain assays provided the only serologic marker of LCDD and served as a marker during treatment



Serum Free Light Chain Assays Predict CR Earlier than SPEP

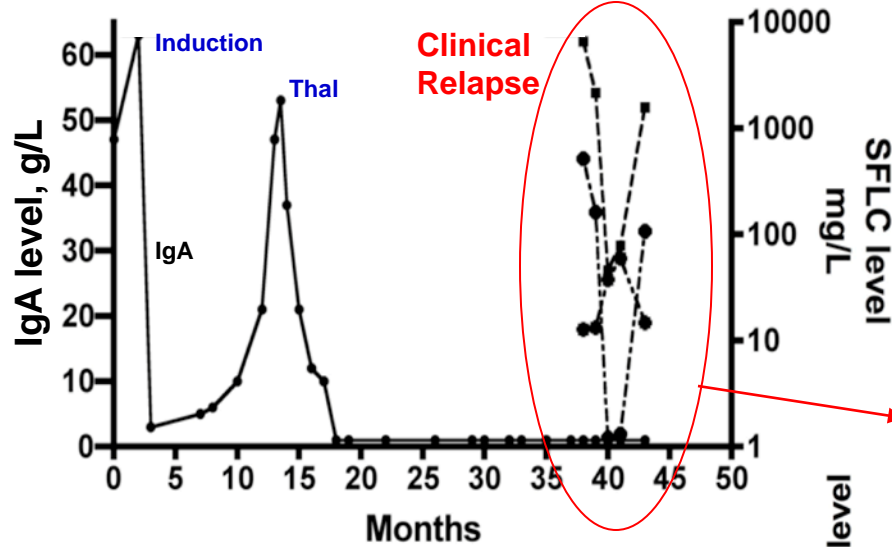
- Stage II/III MM, N = 42 at Memorial Sloan Kettering¹
- Dox/Dex 2–3 cycles → thal/dex 2 cycles
- Serum free light chain assays performed q cycle
- RR 91%
 - 7 CR, 9 nCR, 22 PR
 - Normalization of serum free light chain ratio after 1 or 2 cycles was significantly associated with subsequent CR or nCR ($P = 0.003$)
 - May allow addition of alternative treatment at an early stage if free light chain ratio remains abnormal

Rapid Detection of Relapse With Serum Free Light Chain Assays Versus sIFE

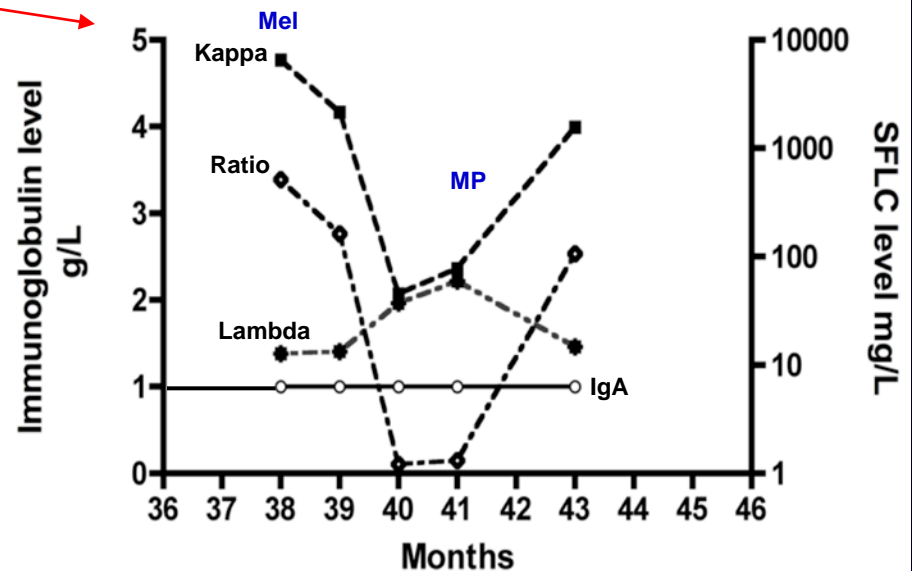


4-mo Earlier Indication of Relapse than sIFE

Extramedullary Relapse With Free Light Chain Escape



Kappa FLC Escape



International Uniform Response Criteria in Myeloma

New!

- Stringent CR
 - Normal free light chain ratio
 - Absence of clonal PC in BM by IHC or IF
- Complete response (CR)
 - Serum and urine IFE negative
 - BM bx \leq 5% PC
 - Disappearance of soft tissue plasmacytoma
 - Normalization of FLC ratio in pts not measurable using above 2 methods

New!

- VGPR
 - IF positive but SPEP negative – or –
 - \geq 90% \downarrow in serum M-protein, and urine M-protein $<$ 100 mg/24 h

- Partial response (PR)
 - \downarrow in serum M-protein by \geq 50% and
 - \downarrow in urine M-protein by \geq 90% or to $<$ 200 mg/24 h and
 - \downarrow in plasmacytoma size by \geq 50% (if present)
 - Non-secretory MM: \geq 50% \downarrow in BM PC
 - \geq 50% \downarrow in difference between involved and uninvolved [sFLC]

New!

- Stable disease: not meeting criteria for CR, sCR, PR or PD

Serum Free Light Chain Assays

- Sensitive, specific, high affinity assays for free kappa and free lambda light chains
- Widely available from reference laboratories and major medical centers
- Ratio
 - Normal in control (general population)
 - Normal in most patients with polyclonal gammopathy
 - Remains normal with mildly impaired renal function; “kappa creep” may be observed with severe CKD
- Highly sensitive for the detection of myeloma, light chain myeloma, oligosecretory myeloma, AL amyloidosis, and light chain deposition disease
- Fully integrated into the diagnostic and response algorithms by the International Myeloma Working Group
- Optimal serum panel for primary evaluation: serum free light chain assays in combination with SPEP or sIFE
- Monitoring for response to treatment and for relapse: earlier indication of response to treatment and of relapse than other testing methods