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The Role of Free Light Chain Measurement in the Management of Multiple Myeloma

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Disclosure of Financial Relationships

Jerry A. Katzmann, Ph.D.

NO, neither I nor my spouse/partner have anything to disclose.

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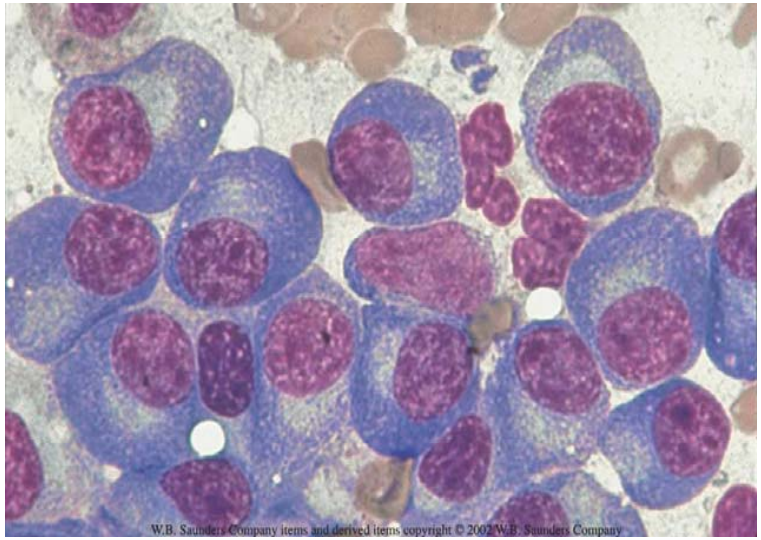

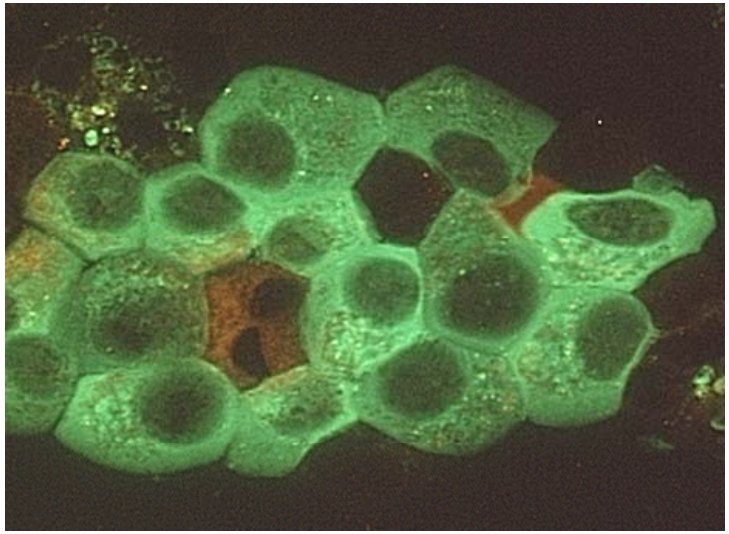

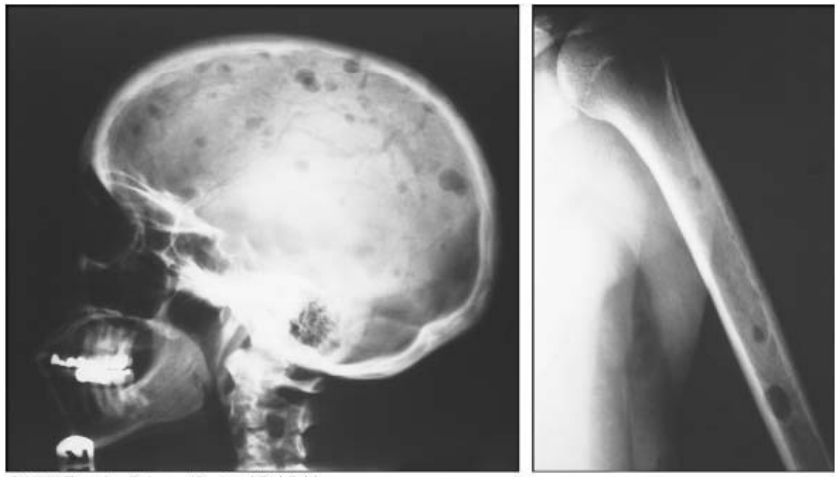

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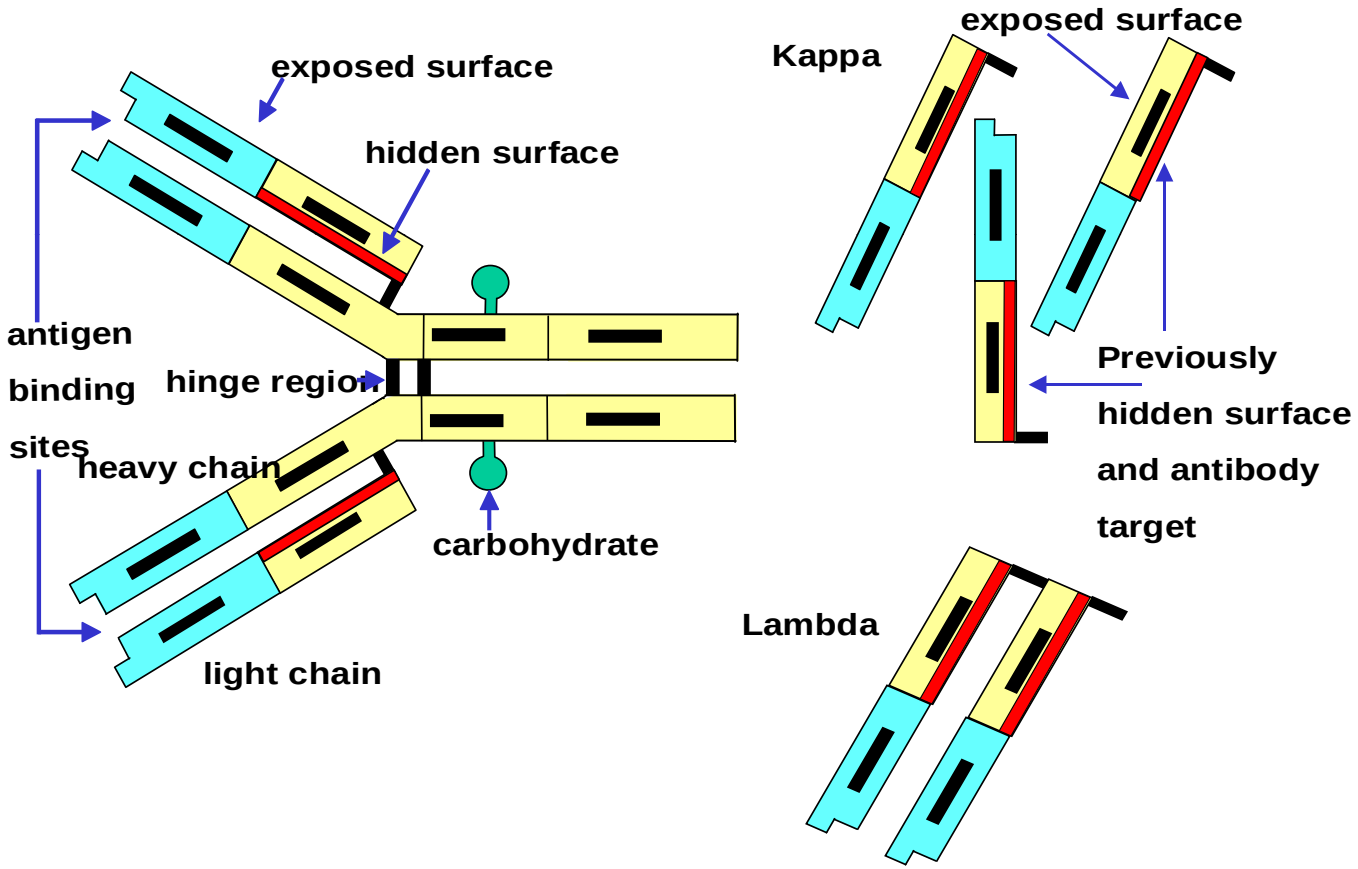
Free Light Chain: Antibody Specificity



The Binding Site, Ltd.

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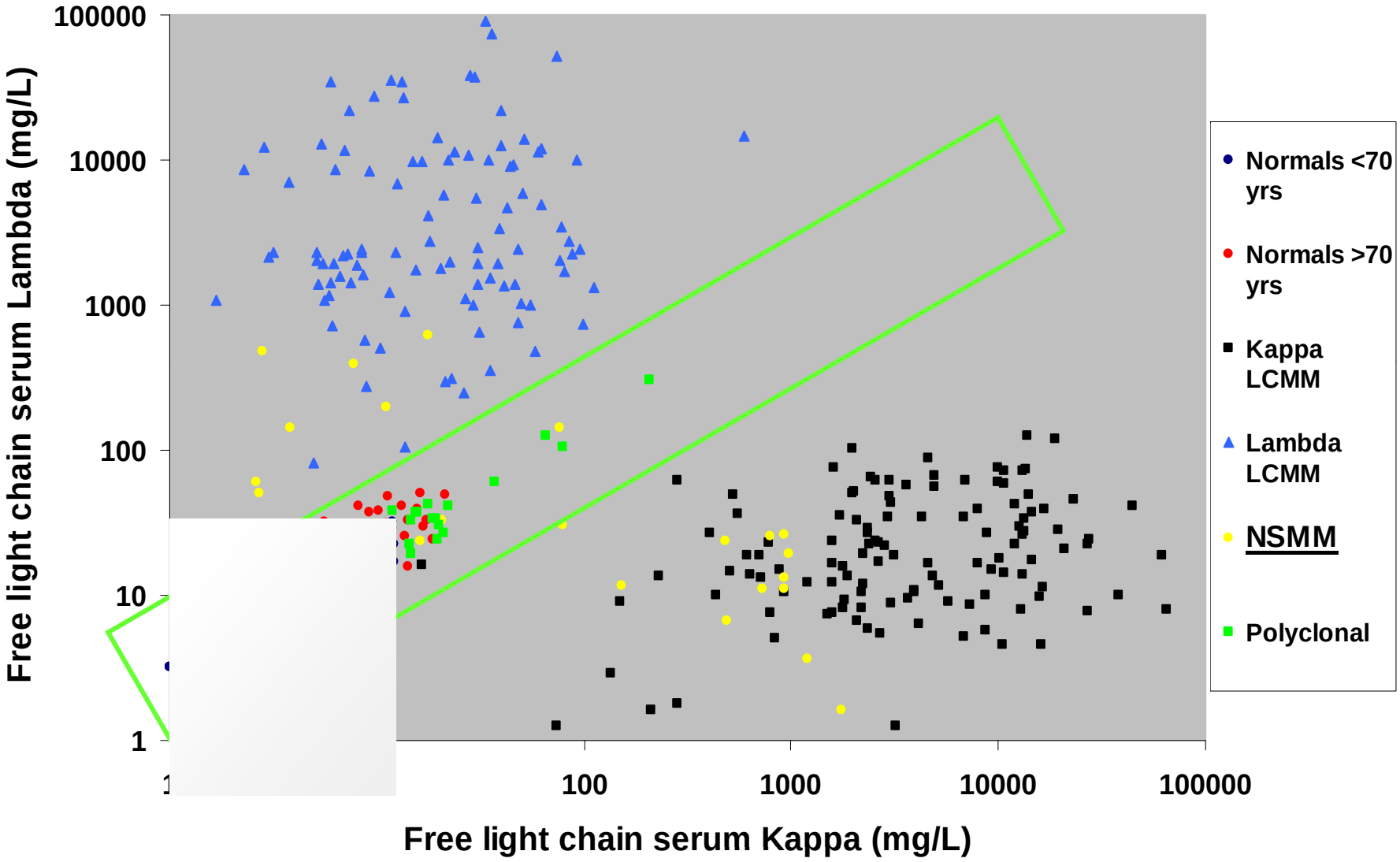

Drayson, et al, Blood, 2001

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International Myeloma Working Group (IMWG) Guidelines for Serum FLC analysis in MM and Related Disorders

- **Diagnosis:**
  - **Screening panel = serum PEL +IFE + FLC.**

    No need for urine studies except if suspected AL

    (*If a PCD is diagnosed, urine studies needed*)
- **Prognosis:**
  - **FLC is prognostic in every PCD studied (MGUS, SMM, MM, AL, solitary plasmacytoma), and baseline values should be measured.**
- **Monitoring:**
  - **Oligosecretory PCD (AL, NSMM, LCDD, …)**
  - **Stringent complete response in multiple myeloma**

Leukemia, Nov. 2008; 1-10

Sensitivity of Monoclonal Gammopathy Screening Panels

Diagnosis	No.	Serum PEL + IFE + FLC Urine IFE	Serum PEL + IFE + Urine IFE	Serum PEL + IFE + FLC	Serum PEL + FLC	Serum IFE	Serum PEL	Serum FLC
All	1,877	1,851	1,821	1,828	1,770	1,632	1,482	1,395
Multiple myeloma	467	467	461	467	467	441	409	452
Macroglobulinemia	26	26	26	26	26	26	26	19
Smoldering MM	191	191	191	191	190	188	180	155
MGUS	524	524	524	509	465	486	429	222
Plasmacytoma	29	26	26	26	23	21	21	16
POEMS	31	30	30	30	23	30	23	3
Extramedullary myeloma	10	2	2	1	1	1	1	1
Primary amyloid	581	570	547	564	559	429	383	513
Lt chain deposition	18	15	14	14	14	10	10	14

3001466B-4

Katzmann et al, Clin Chem, 2009

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IMWG Guidelines for Quantitative FLC: Impact on the Laboratory

- **Diagnosis:**
  - Screening panel: serum PEL/IFE & FLC unless suspect AL.
    - Serum PEL & FLC is sufficient for initial screen
- **Prognosis:**

  FLC is prognostic in every PCD studied (MGUS, SMM, MM, AL, solitary plasmacytoma), and baseline values should be measured:
  - **MGUS** progression (FLC, PEL, IFE)
  - **Smoldering myeloma** progression (FLC, PEL, %BMPC)
  - **Symptomatic myeloma** survival (FLC, β2M, Alb)
  - **Plasmacytoma** survival (FLC, IFE at 1 yr)
  - **AL amyloidosis** survival (FLC response)

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A Long Term Study of Prognosis in MGUS

1384 patients in SE MN were identified with MGUS between 1960 and 1994. Patients were followed for an average of 8 years (11,009 total patient years).

115 progressed to MM, lymphoma, AL, Macroglobulinemia, CLL, or plasmacytoma

~1% of MGUS patients progress/year.

Initial size of M-spike and heavy chain isotype are prognostic for progression

Kyle, et al, NEJM, 2002

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Free Light Chain Quantitation

	% Abnormal Serum	
	FLC mg/dL (κ or λ)	κ/λ Ratio
LCMM	100%	100%
MM	73%	92%
SMM	64%	96%
MGUS (•→MM)	30%	67%
MGUS (stable)	22%	22%

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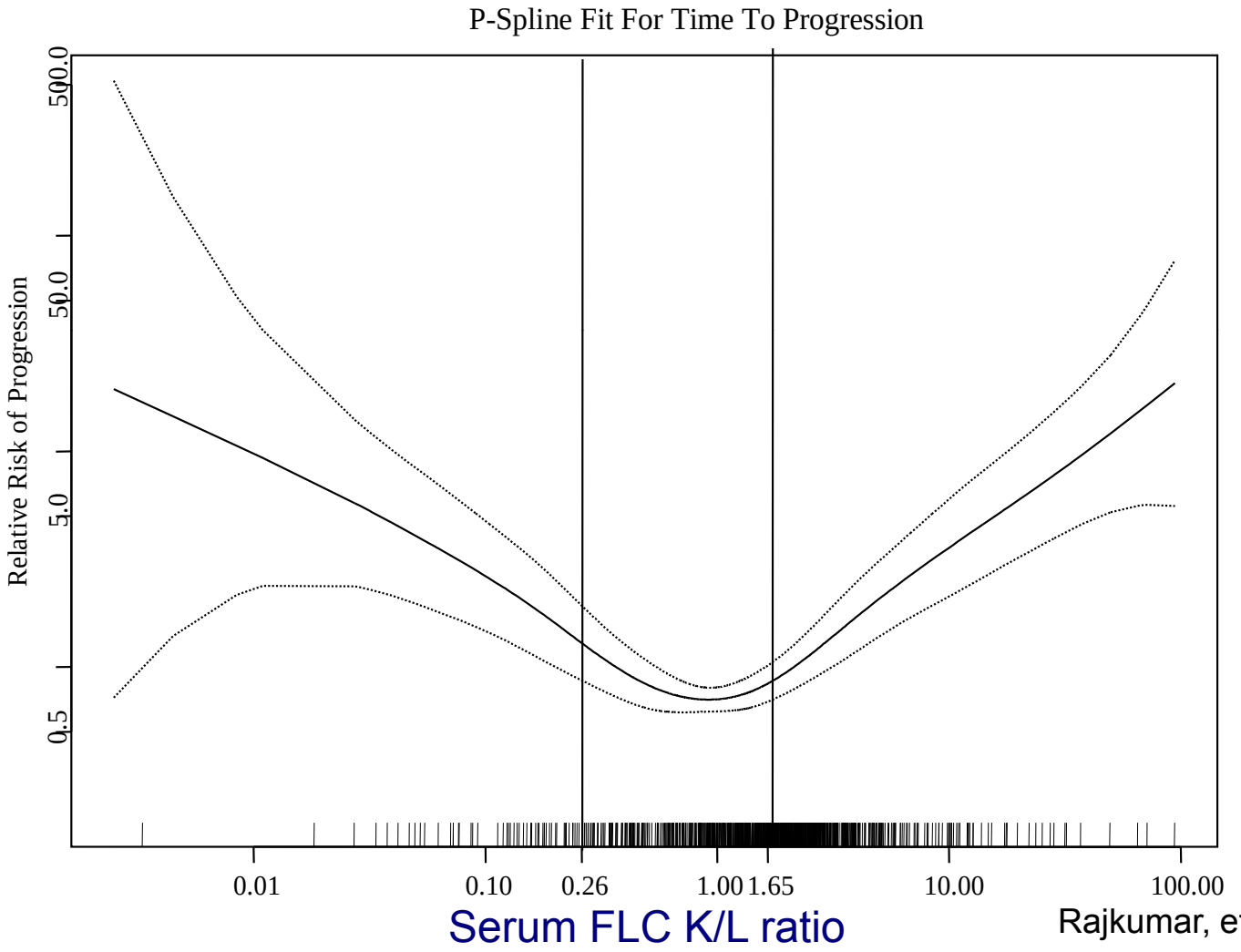
Population Based Cohort Study: Impact of FLC



Rajkumar, et al, Blood, 2005

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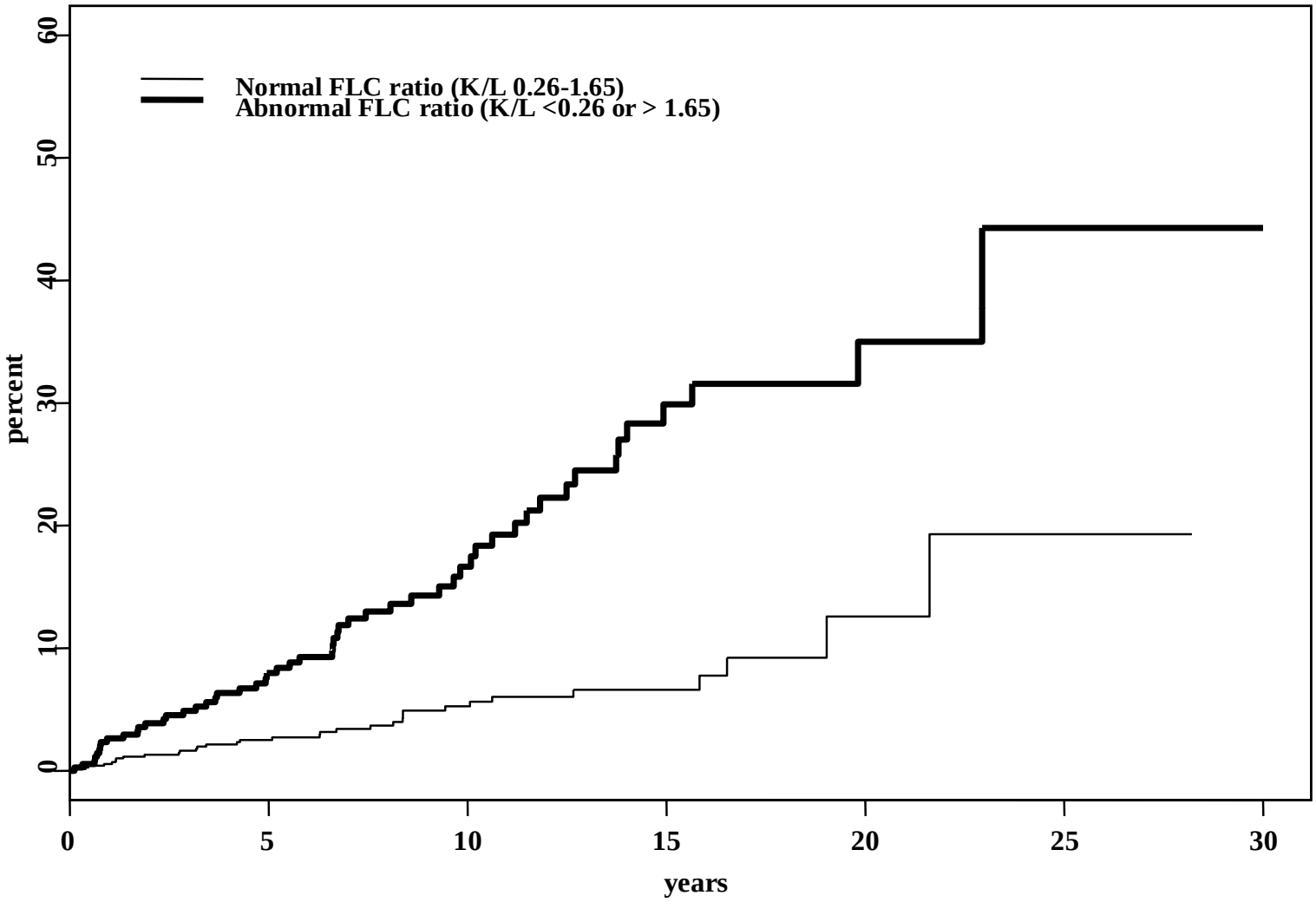
FLC and Progression in MGUS



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Multivariate Analysis of Prognostic Factors for Progression of MGUS

Prognostic factor	Hazard ratio (95% C.I.)	p value
Abnormal FLC ratio	2.6 (1.7,4.2)	<0.001
Serum M protein size	2.4 (1.7,3.5)	<0.001
IgA, IgM, or biclonal IgA plus IgM	2.6 (1.7,4.0)	<0.001

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Risk stratification model incorporating all 3 predictive factors

Risk Group	# of pts.	Relative risk	20 year risk of prog. (after other causes of death)
1. Low-risk (Serum M protein <1.5 gm/dL, IgG subtype, normal FLC ratio)	449 (39%)	1	2%
2. Lo/Intermediate-risk (Any 1 factor abnormal)	420 (37%)	5.4	10%
3. Hi/Intermediate-risk (Any 2 factors abnormal)	226 (20%)	10.1	18%
4. High-risk (All 3 factors abnormal)	53 (5%)	20.8	27%

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Prognosis: FLC Ratio Depends on Disease

Diagnosis	FLC ratio (reference range)
MGUS	0.26 - 1.65
Plasmacytoma	0.26 - 4.0
Smoldering myeloma	0.125 - 8
Symptomatic myeloma	0.03 - 32

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International Myeloma Working Group Guidelines for quantitative FLC

- **Diagnosis:**
  - **Screening panel: serum PEL (+IFE) + FLC.**
    No need for urine studies except if suspected AL
    (If a PCD is diagnosed, urine studies needed)
- **Prognosis:**
  - **FLC is prognostic in every PCD studied (MGUS, SMM, MM, AL, solitary plasmacytoma), and baseline values should be measured.**
    - ***Progressively abnormal rFLC from MGUS to MM discriminate good/poor prognosis.***
- **Monitoring:**
  - **Oligosecretory PCD (AL, NSMM, LCDD, …)**
  - **Stringent complete response in multiple myeloma**

Dispenzieri et al, Leukemia, 2009

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Response Criteria for FLC

	PR	CR	sCR	Prog
No measurable disease[1]				
AL	iFLC[2] ↓ 50%	Nl rFLC & CR by IFE & BM	ND	iFLC ↑ 50% (> 100 mg/L)
MM	dFLC[2] ↓ 50%		Nl rFLC & CR by IFE & BM	↑ 50% dFLC
Measurable disease[1]				
MM			Nl rFLC & CR by IFE & BM	

[1] Measurable includes serum M-protein ≥ 10 g/L or a urine M-protein ≥ 200 mg/day for myeloma patients (100 mg/day for AL patients).

[2] iFLC = involved FLC; dFLC = FLC difference (involved-uninvolved)

Gertz MA et al. Am J Hematol. 2005;79:319-328.
Durie BG et al. Leukemia. 2006;20:1467-1473.

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Disease monitoring:

Coefficient of Variation (CV) of serial samples

Stable disease[a]	IgG Quant	SPEP M-spike[b]	Involved FLC[c]	UPEP M-spike[d]
MGUS	10.2% [n=35]	7.8% [n=18]	55.2% [n=10]	57.9% [n=1]
SMM	8.1% [n=48]	3.9% [n=41]	26.2% [n=10]	45.4% [n=5]
MM	8.5% [n=60]	7.6% [n=23]	38.9% [n=19]	37.3% [n=5]

[a] Stable disease = no disease progression + for SMM & MM at least 4 assays within 9-15 months with M-spikes all within 0.5 g/dL or for MGUS at least 4 assays within 5 years with M-spikes all within 25%.

[b] M-spike > 1 g/dL

[c] abnormal K/L ratio and involved FLC > 10 mg/dL

[d] M-spike > 200 mg/24 hr.

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IMWG Guidelines for quantitative FLC: Impact on the Laboratory

- **Diagnosis:**
  - Screening panel: serum PEL/IFE & FLC.
    - **Do we need IFE?**
      Serum PEL & FLC are sufficient for MM screen.
- **Prognosis:**
  - FLC is prognostic in every PCD studied (MGUS, SMM, MM, AL, solitary plasmacytoma), and baseline values should be measured.
    - **What values discriminate good/bad prognosis?**
      Progressively abnormal rFLC from MGUS to MM.
- **Monitoring:**
  - Oligosecretory PCD (AL, NSMM, LCDD…) and stringent CR
    - **Can serum FLC replace urine?**
      ??