

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)

**ASH/FDA Workshop on Clinical
Endpoints in Multiple Myeloma**

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MGUS

Olmsted County MN

Criteria

- Serum M-spike < 3.0 g/dL
- Bone marrow plasma cells <10% if done
- No evidence of other B-cell disorders
- No end organ damage

MGUS OLMSTED COUNTY, MN

RESULTS

- Olmsted County Residents \geq 50 years; 28,038
- Serum samples obtained from population: 77%

Kyle et al., New Engl J Med, 2006, 354:1362

MGUS

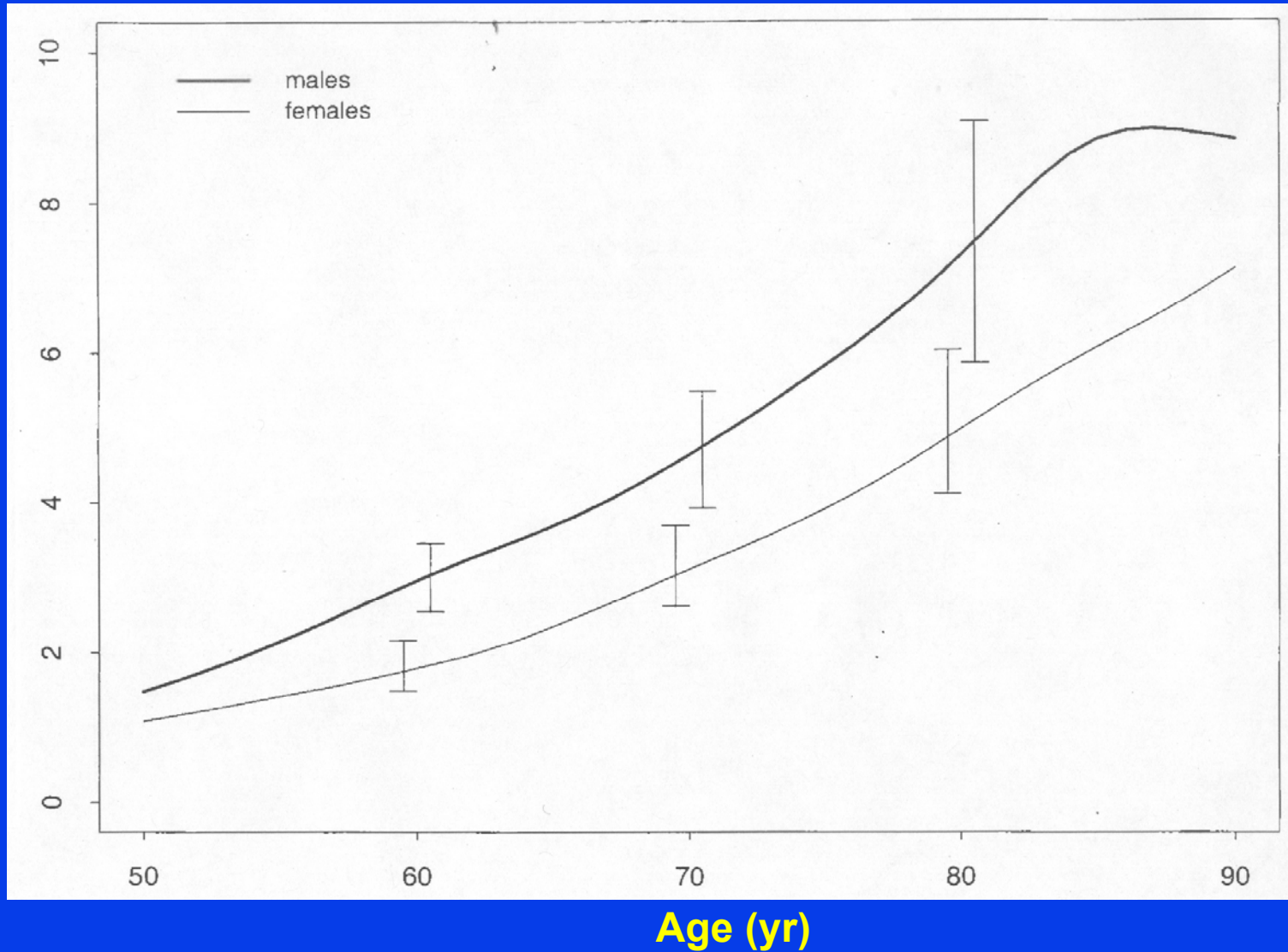
Olmsted County MN

Age	No.	M-protein	
		No.	%
50 – 59	8,373	141	1.7
60 – 69	6,019	178	3.0
70 – 79	4,508	205	4.6
≥80	2,563	170	6.6
Total	21,463	694	3.2
≥ 70	7,071	375	5.3

Kyle et al., New Engl J Med, 2006, 354:1362

Prevalence of MGUS According to Age

Prevalence of MGUS (%)



MGUS in African Americans

	White	African American
N Subjects	3,250,107	749,754
MGUS N, %	1,312 (.40%)	734 (.98%)
MM at 10 yrs	15%	17%

Langren, et al., Blood, 107:904, 2006

MGUS

SE Minnesota

Jan 1, 1960-Dec 31, 1994

n=1,384

Male (%)	54
Age (med years)	72
<40 years (%)	1.7
M-spike (g/dL-med)	1.2

Kyle, et al., New Engl J Med, 346:564, 2002

MGUS SE MINNESOTA

Relative Risk of Progression

	Obs	Exp*	RR
Multiple Myeloma	75	3	25
Lymphoma, IgM	19	7.8	2.4
Amyloidosis	10	1.2	8.4
Macroglobulinemia	7	0.2	46
CLL	3	3.5	0.9
Plasmacytoma	1	0.1	8.5
Total	115	15.8	7.3

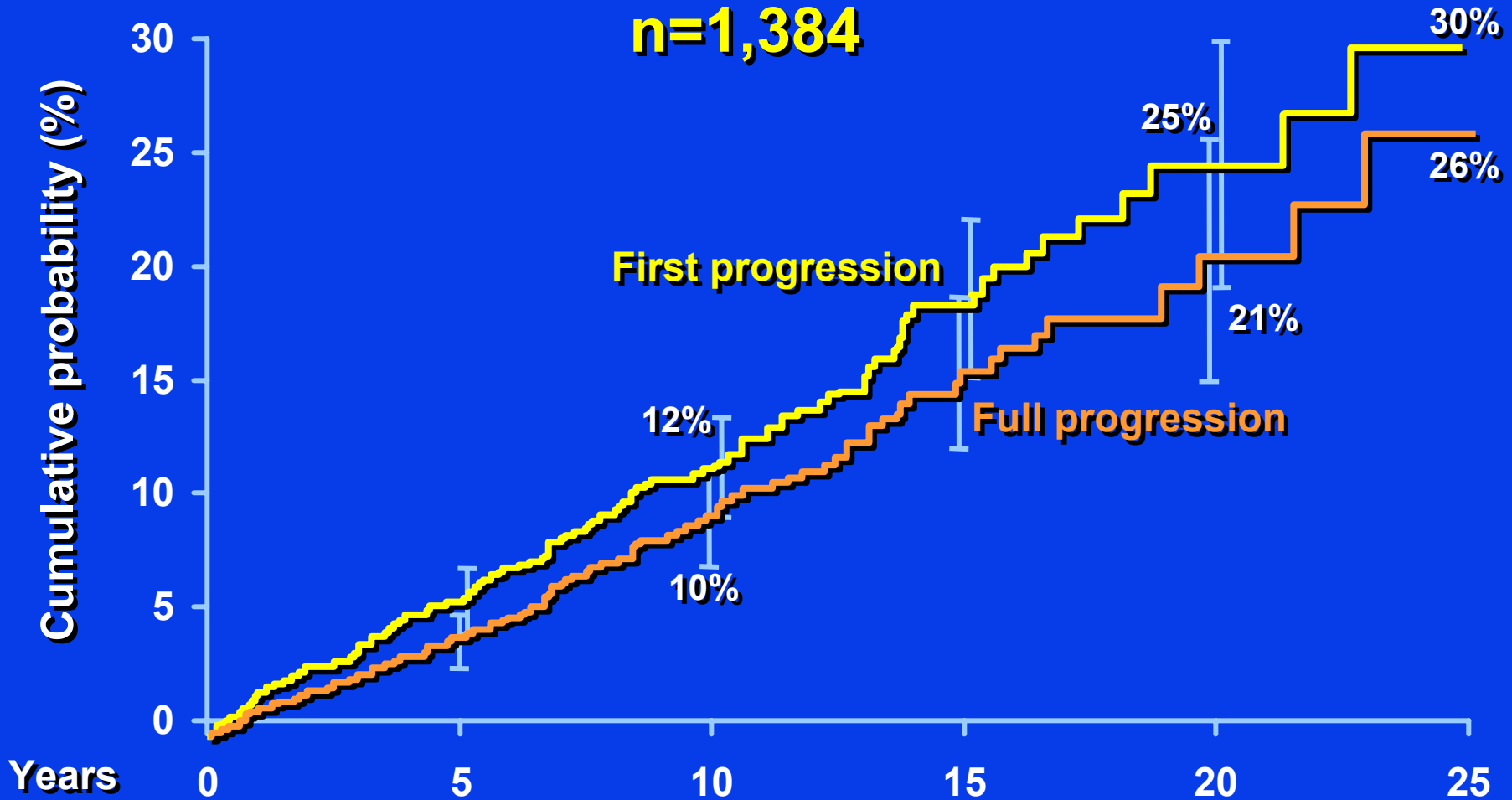
* Iowa SEER Registry

Kyle, et al., New Engl J Med, 346:564, 2002

MGUS SE Minnesota

1960-1994

n=1,384



Patients at risk

1,384

867

423

177

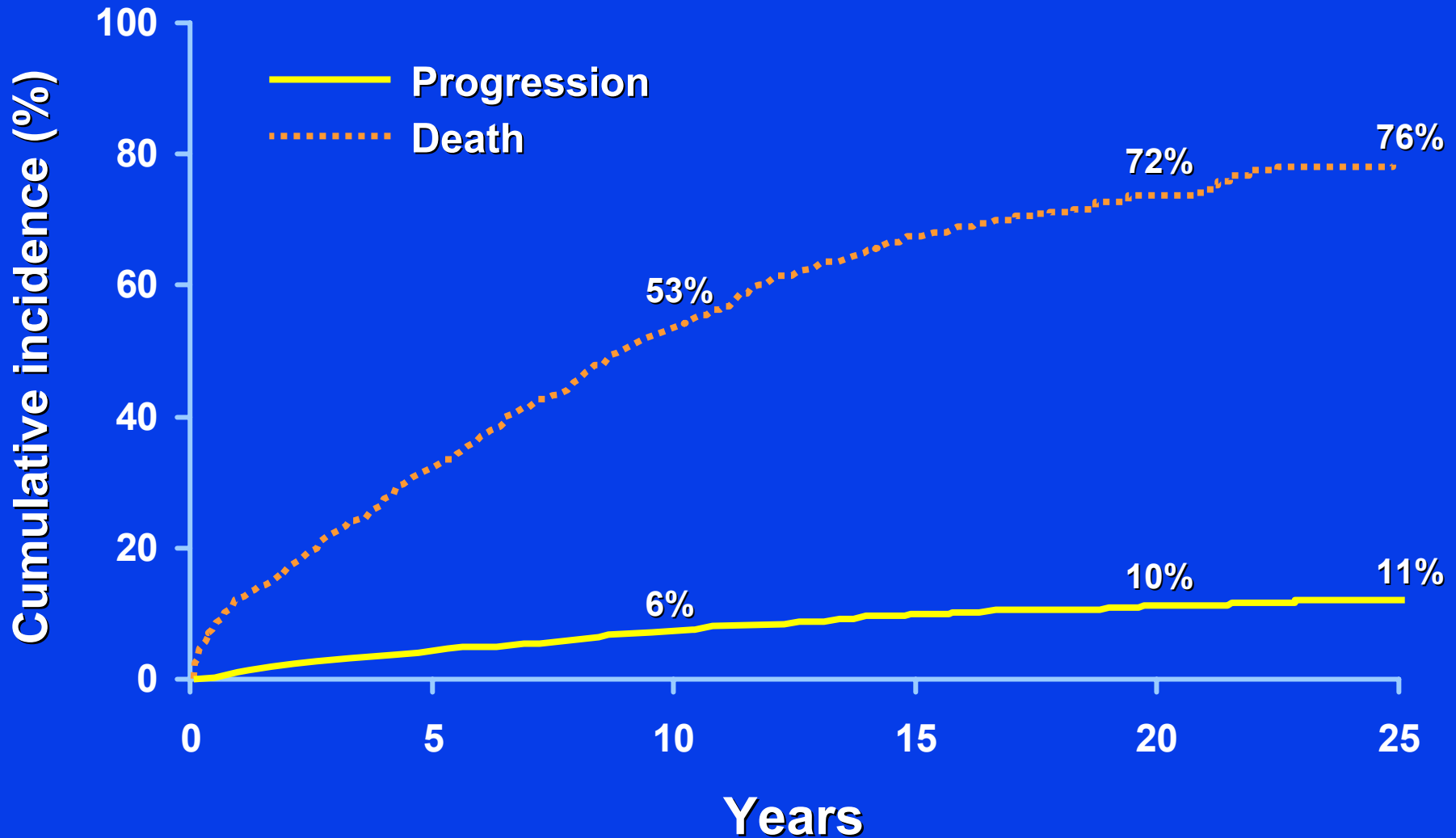
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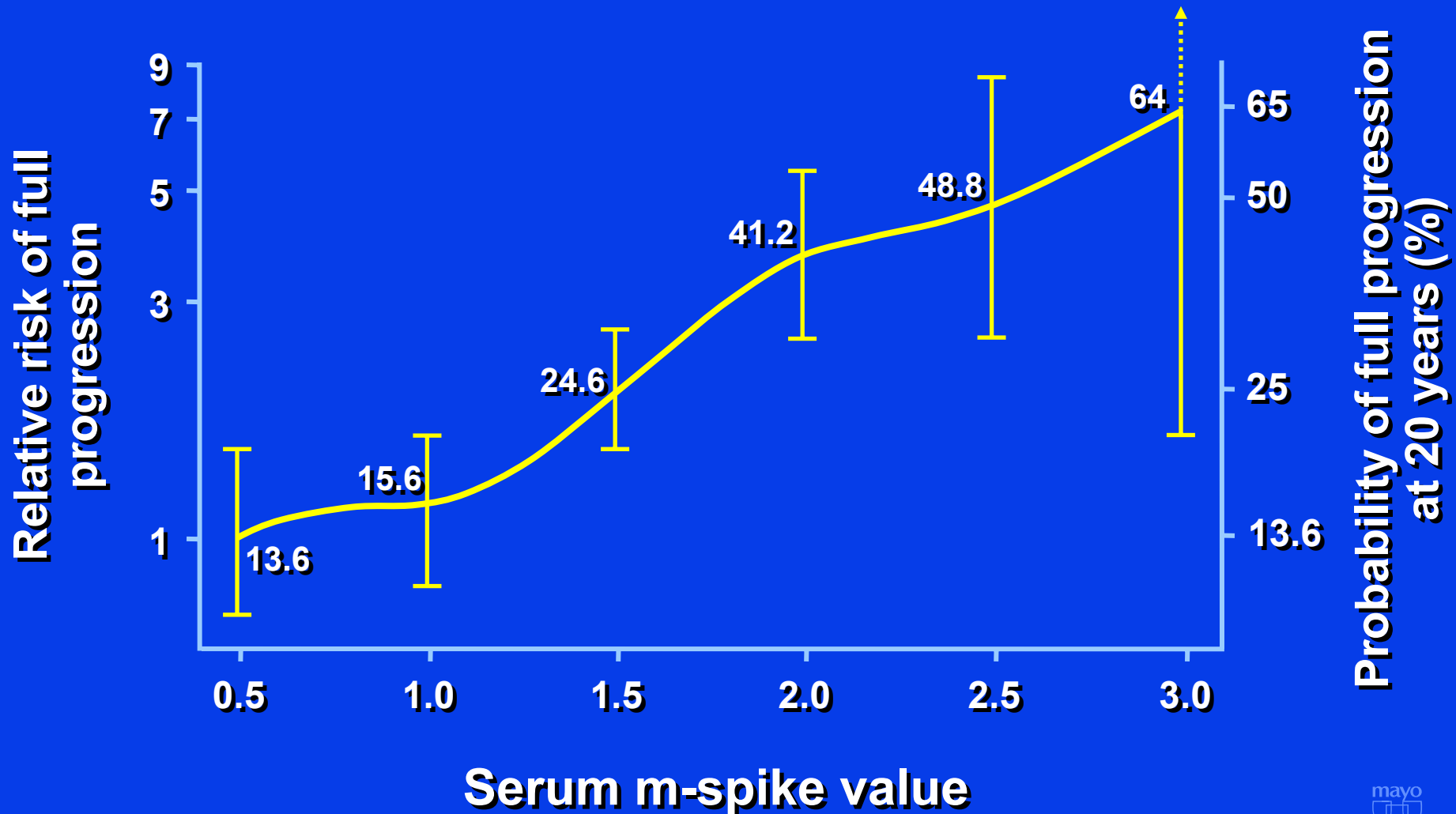


Kyle, et al., New Engl J Med, 346:564, 2002

Full Progression or Death



Relative Risk of Full Progression by Serum M-Spike Size



Kyle, et al., New Engl J Med, 346:564, 2002

MGUS and Free Light Chain (FLC)

	N	RR	Risk of Prog	
		95% CI	20 yr	
			Absolute	Competing risk
			%	
M-protein < 1.5 g/dl, IgG, Normal FLC	449	1	5	2
1 risk factor, abn	420	5.4	21	10
2 risk factors, abn	226	10.1	37	18
3 risk factors, abn	53	20.8	58	27

Rajkumar, et al., Blood; 106:1148, 2005

Smoldering Multiple Myeloma

- Serum M-spike ≥ 3 g/dl
- and
- Bone marrow plasma cells $\geq 10\%$
- No end organ damage

Kyle RA and Greipp PR, NEJM, 302:1347, 1980.

Smoldering Multiple Myeloma

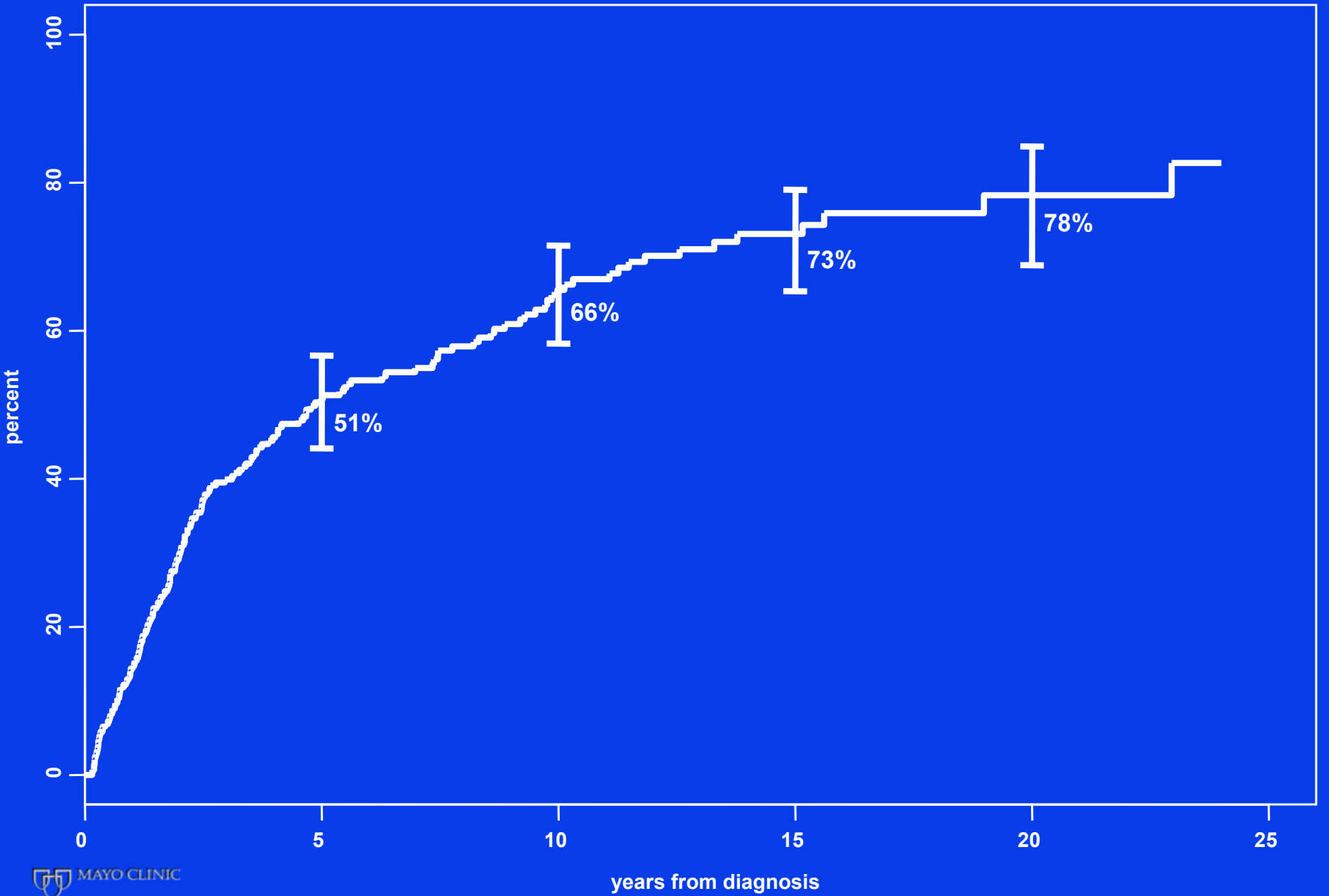
Mayo Clinic 1970 – 1994

	N	%
Serum M-protein \geq 3 g/dl and Bone marrow plasma cells \geq 10%	113	38
Serum M-protein $<$ 3 g/dl and Bone marrow plasma cells \geq 10%	158	52
Serum M-protein \geq 3 g/dl and Bone marrow plasma cells $<$ 10%	30	10
TOTAL	301	100

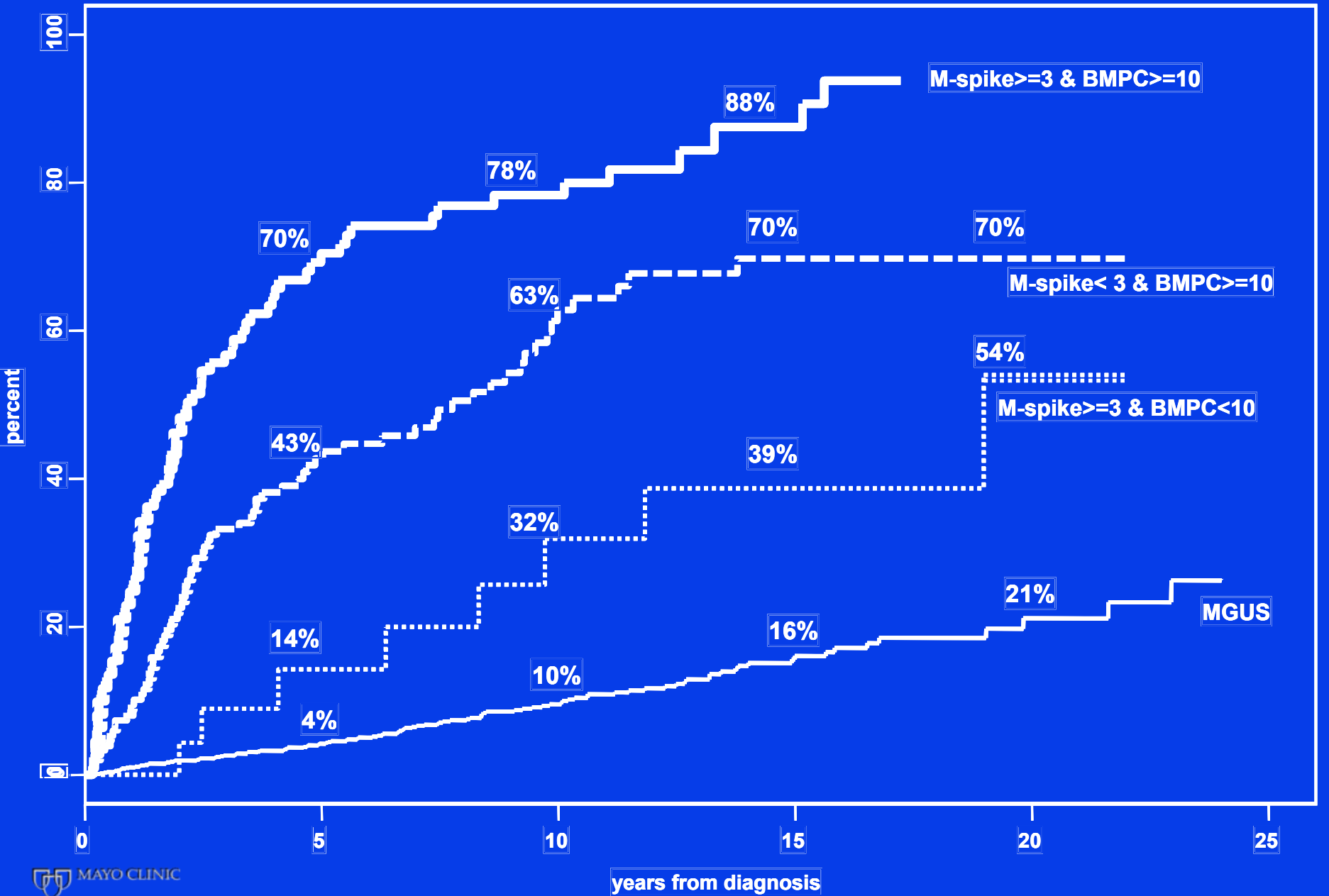
Smoldering Multiple Myeloma

Time to progression	Median years
Serum M-spike ≥ 3 Bone marrow plasma cells ≥ 10	2.2
Serum M-spike < 3 Bone marrow plasma cells ≥ 10	7.8
Serum M-spike ≥ 3 Bone marrow plasma cells < 10	19
Total (N = 301) p= <0.001	5.5

Progression to Multiple Myeloma or Amyloid



Progression to MM or AL



MGUS and SMM

Standard of Care:

Defer Treatment Until End Organ
Damage

- C** **Hypercalcemia**
- R** **Renal Insufficiency**
- A** **Anemia**
- B** **Bone disease**

MGUS and SMM

**Therapy justified only if
preventative strategy
prolongs survival**

MGUS Question

- 1. How often should the patient be monitored?**
- 2. Should “high risk” MGUS be treated?**
- 3. Why is MGUS increased in African-Americans?**

SMM Question

- 1. Should SMM have both M spike \geq 3g/dl and plasma cells \geq 10%.**
- 2. Should SMM be treated?**
- 3. Does reduction of M spike and plasma cells delay progression?**

MGUS/SMM Subcommittee

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