Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM): *The Key*  *to Neoplasia*

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MAYO CLINIC

DISCLOSURE

Relevant Financial Relationship:

None

Off Label Usage:

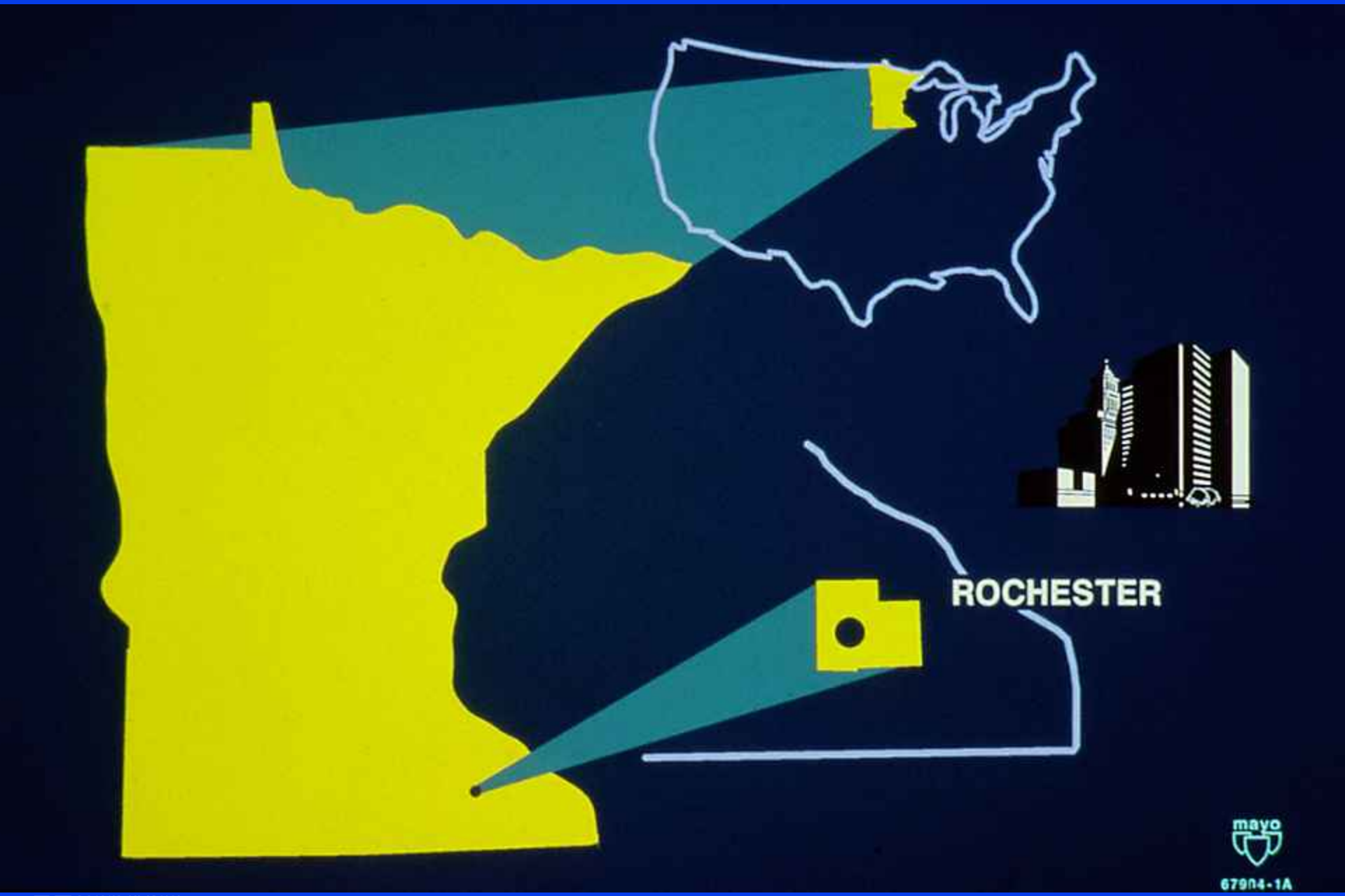
None

Monoclonal Gammopathy of Undetermined Significance

- Prevalence
- De novo multiple myeloma
- Recognition of MGUS in practice
- Duration of MGUS before recognition

Monoclonal Gammopathy of Undetermined Significance: Prevalence ≥50 Years

Site of Study	*Subjects (number)*	*With M-proteins (number, %)*
Sweden	3,674	59 (1.6%)
France	17,968	303 (1.7%)
USA	1,200	15 (1.25%)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MGUS: Olmsted County, Minnesota
Inclusion 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, Minnesota
Prevalence Study

- Olmsted County residents ≥50 years: 28,038
- Serum samples obtained from population: 77%

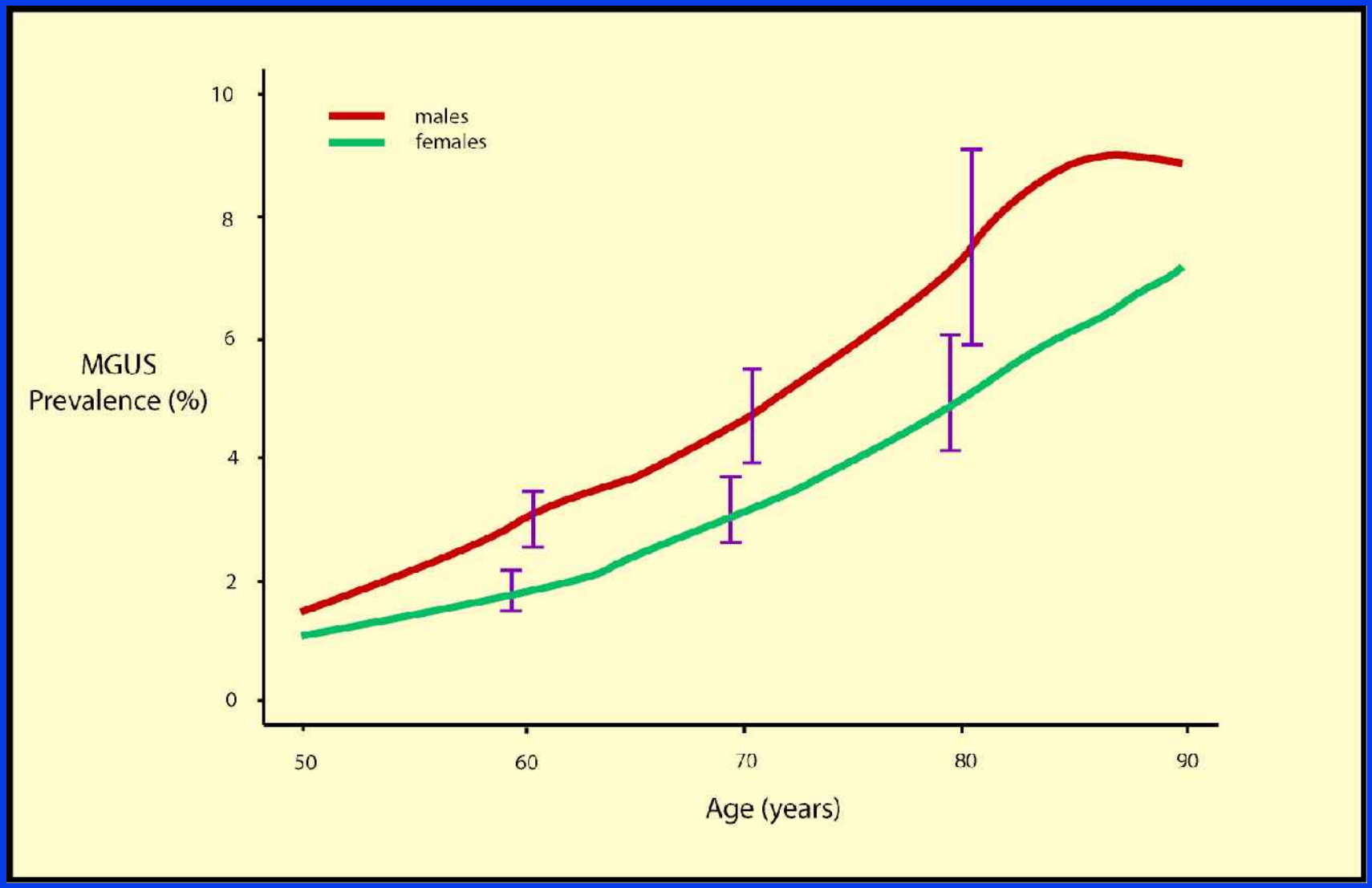
Kyle et al: New Engl J med 354:1362, 2006

MGUS:
Olmsted County, Minnesota

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



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

MGUS
OLMSTED COUNTY MN

Conclusions:

- Prevalence rate remained almost constant throughout collection, suggesting that patients who frequently seek medical care are at little or no greater risk for MGUS than those who do not.

- The prevalence was 4-fold higher in persons ≥80 years of age than those age 50-59 years.

MGUS
OLMSTED COUNTY MN

Conclusions

(continued)

- The prevalence was 2-fold higher than from the literature in persons ≥50 years of age and almost twice that previously reported in persons ≥70 years of age.

- MGUS is one of the most common pre-malignant disorders in the general population ≥50 years of age.

MGUS Precedes MM

PCLO Study

N = 77,469

	N
Developed MM	71

Landgren et al., Blood 113:5412, 2009

MGUS Present Before DX MM

Years	%
2	100
3	98
5	95
7	93
8+	82

Landgren et al., Blood 113:5412, 2009

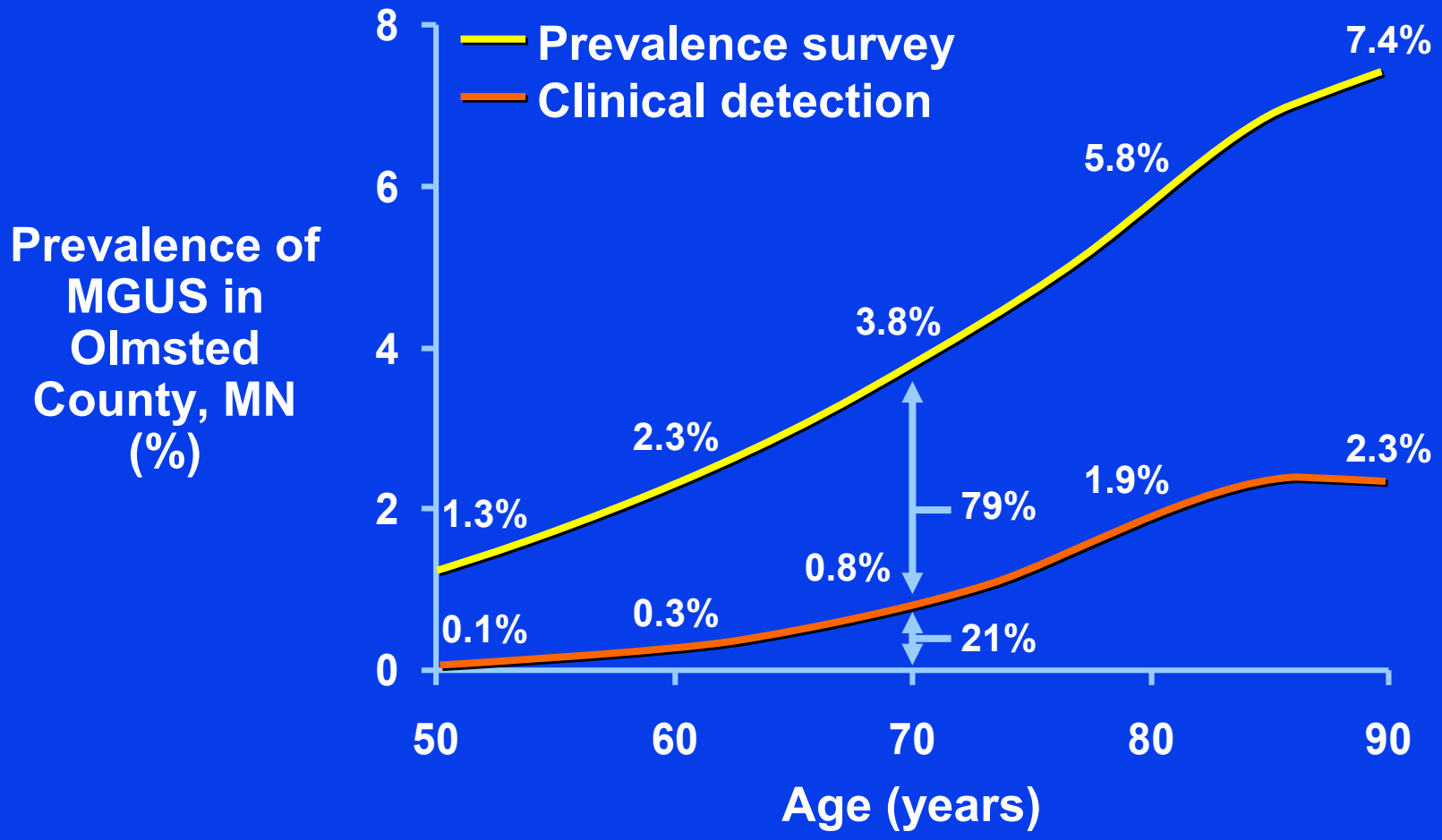
MGUS

Virtually all patients with multiple myeloma have a previously recognized M-protein (MGUS).

MGUS

How many patients with MGUS are recognized during clinical practice at Mayo Clinic?

MGUS: Prevalence in Olmsted County, MN vs Clinical Detection



Kyle et al., Blood, 2007, 110:79a

Prevalence vs Detection of MGUS

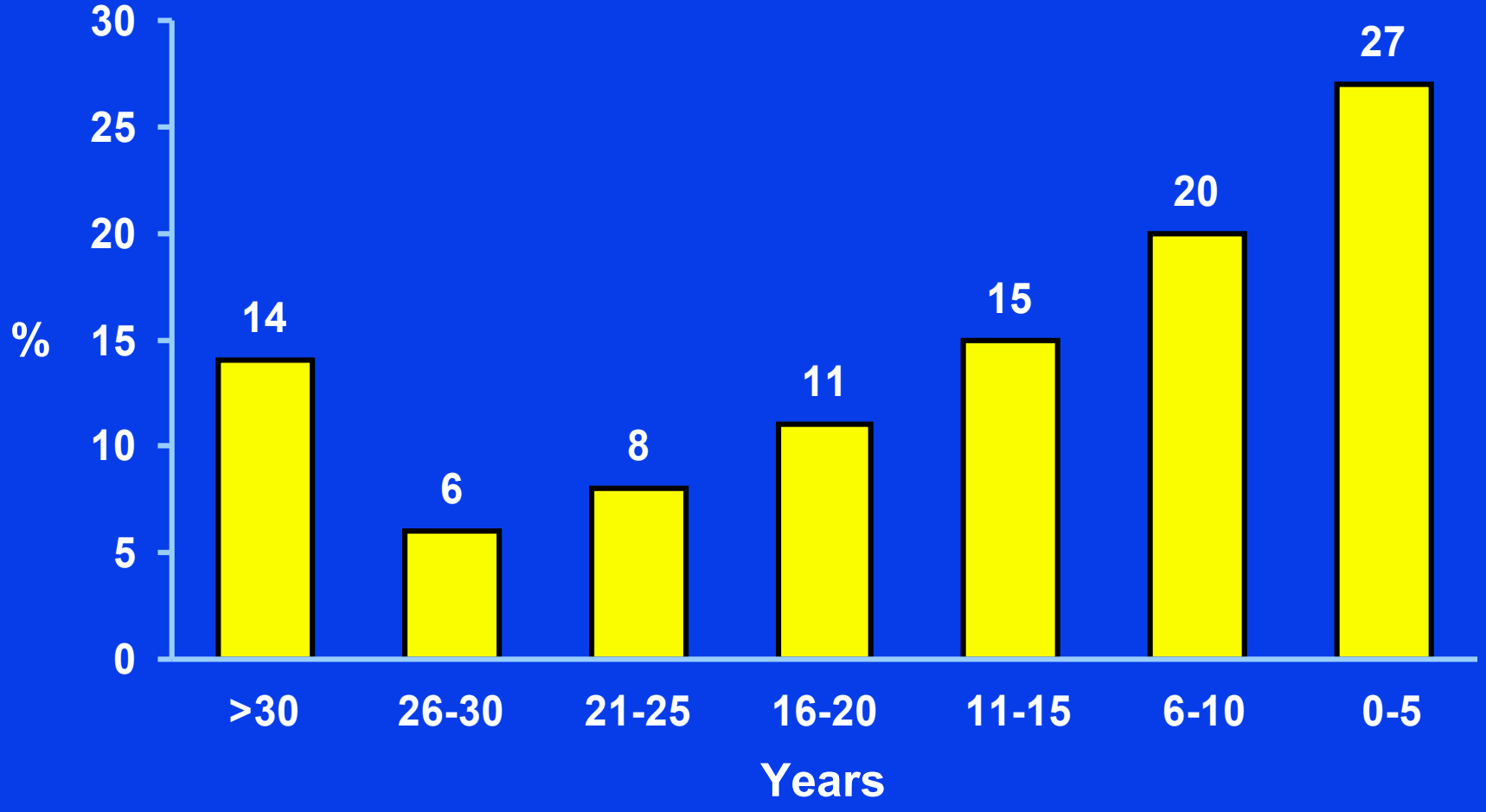
	Prevalence		Clinically detected	
Age	Actual (%)	Clinically detected (%)	Yes (%)	No (%)
50	1.3	0.1	8	92
60	2.3	0.3	13	87
70	3.8	0.8	21	79
80	5.8	1.9	33	67
90	7.4	2.3	31	69
≥50	3.2	0.7	22	78

MAYO CLINIC Kyle et al., Blood, 2007, 110:79a

MGUS

How long has MGUS been present when it is recognized?

Duration of MGUS for A Patient At Age 70



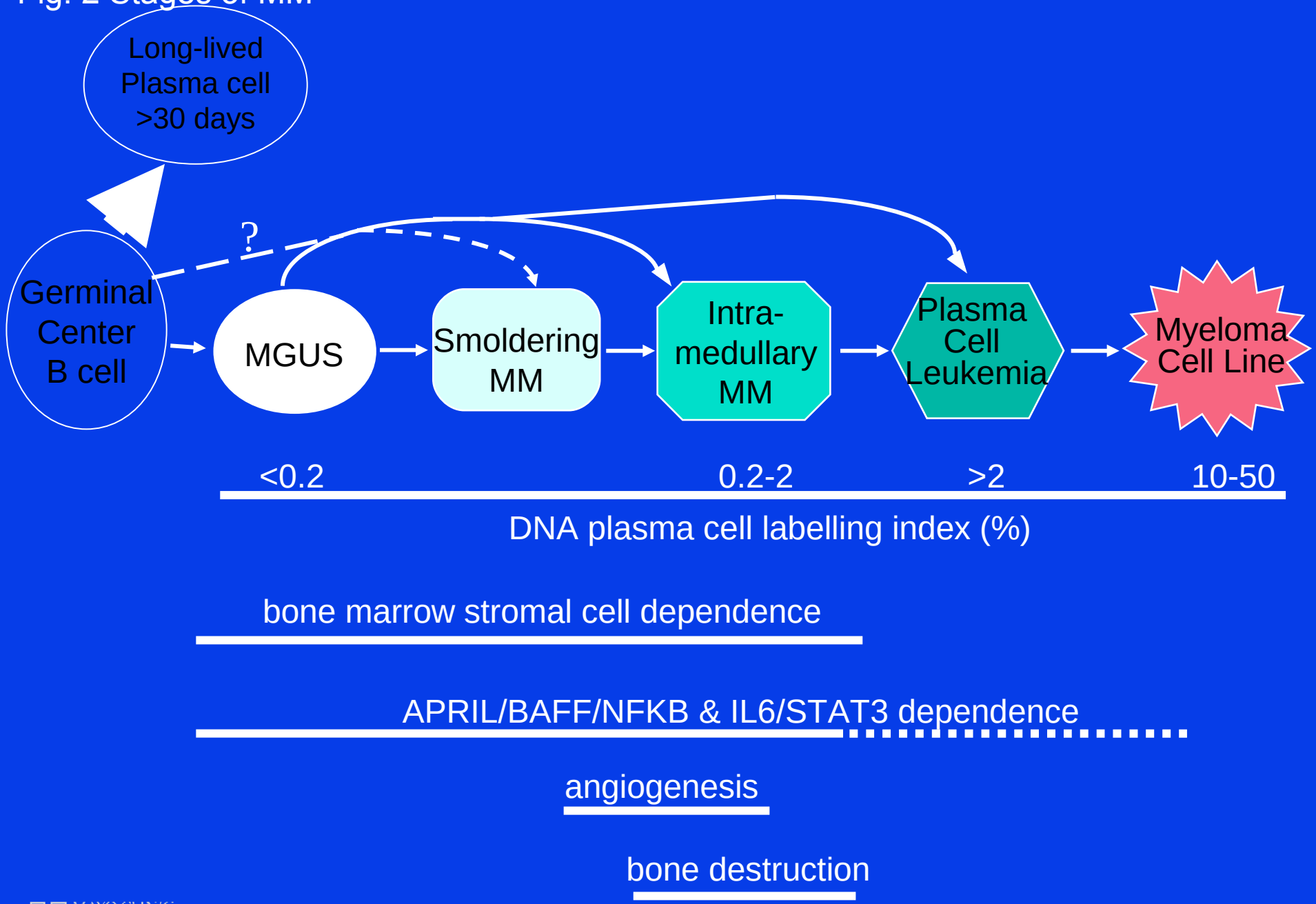
MAYO CLINIC Kyle et al., Blood, 2007, 110:79a

Monoclonal Gammopathy of Undetermined Significance (MGUS): Conclusions

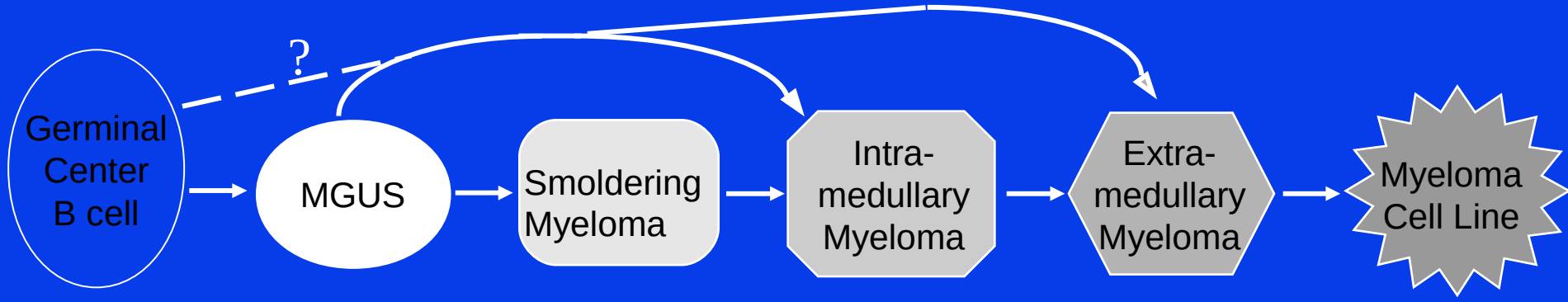
- Only 22% with known MGUS have been recognized clinically
- 28% recognized as MGUS at age 70 have had it >20 years
- Median duration of MGUS prior to its recognition = 11 years

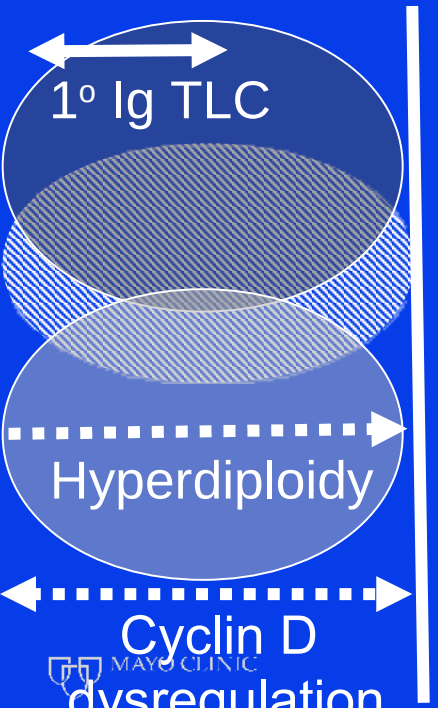
Kyle et al., Blood, 2007, 110:79a

Fig. 2 Stages of MM



Multi-step molecular pathogenesis of MM





MAPK dysregulation: N, K- RAS, FGFR3

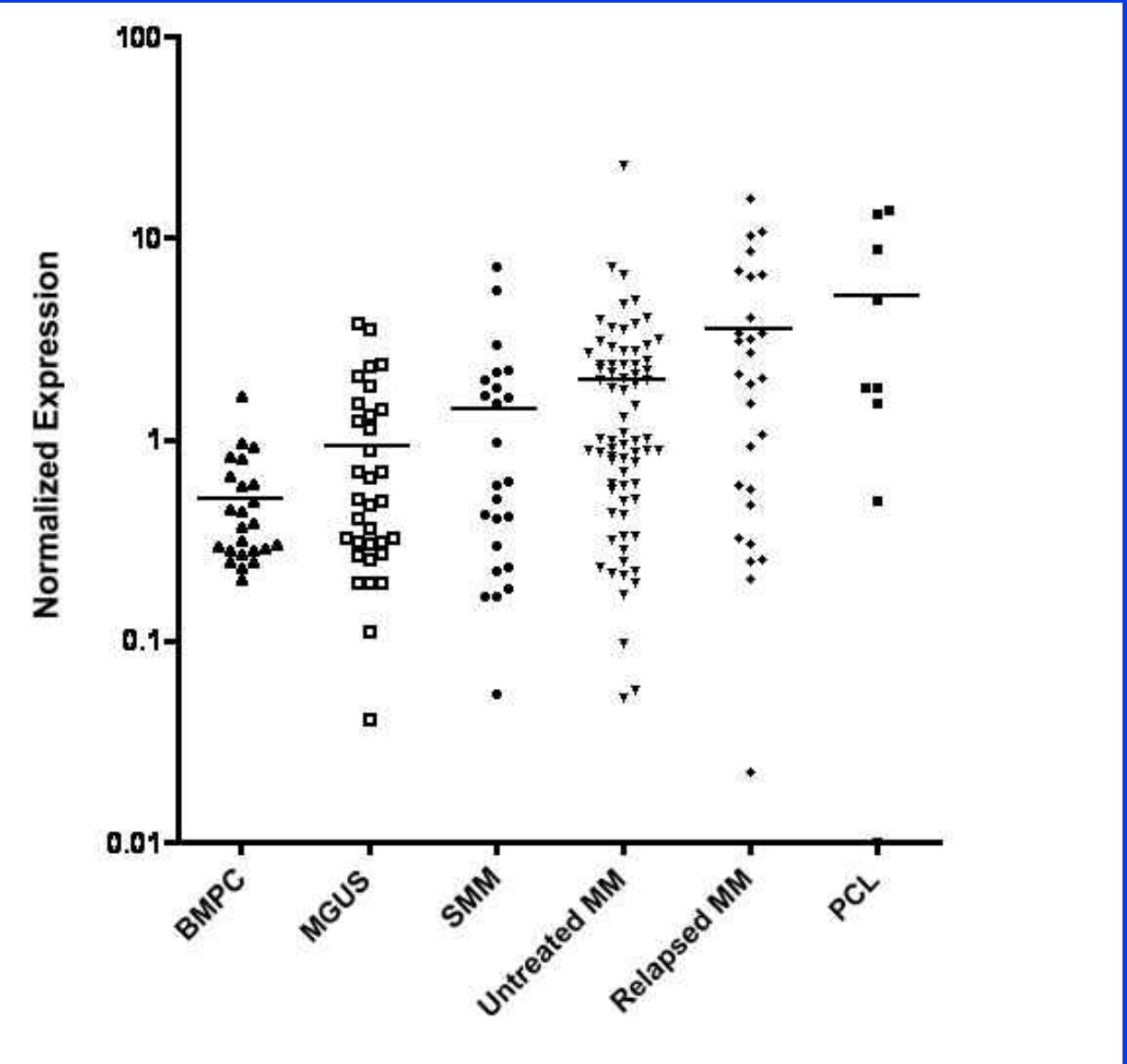
NFkB dysregulation

MYC up-regulation

MYC dysregulation

p53 inactivation

Expression of MYC increases with disease progression



Monoclonal Gammopathy of Undetermined Significance
Natural History in 241 Cases

241 patients with an M-Protein in the serum but initially no evidence of multiple myeloma, macroglobulinemia, amyloidosis, or lymphoma 1956-1970 were followed up.

Kyle RA, Am J Med 64:814, 1978

MGUS
Status at Follow-Up 1-39 Years (241 Cases)

		Follow-up Person-years 3,579 Median	
Group	Description	No.	%
1	No substantial increase of M-protein (benign)	14	6
2	Increase M-protein (≥3 g/dL)	25	10
3	Died of unrelated causes	138	57
4	Development of myeloma, macroglobulinemia, amyloidosis, etc	64	27
Total		241	100

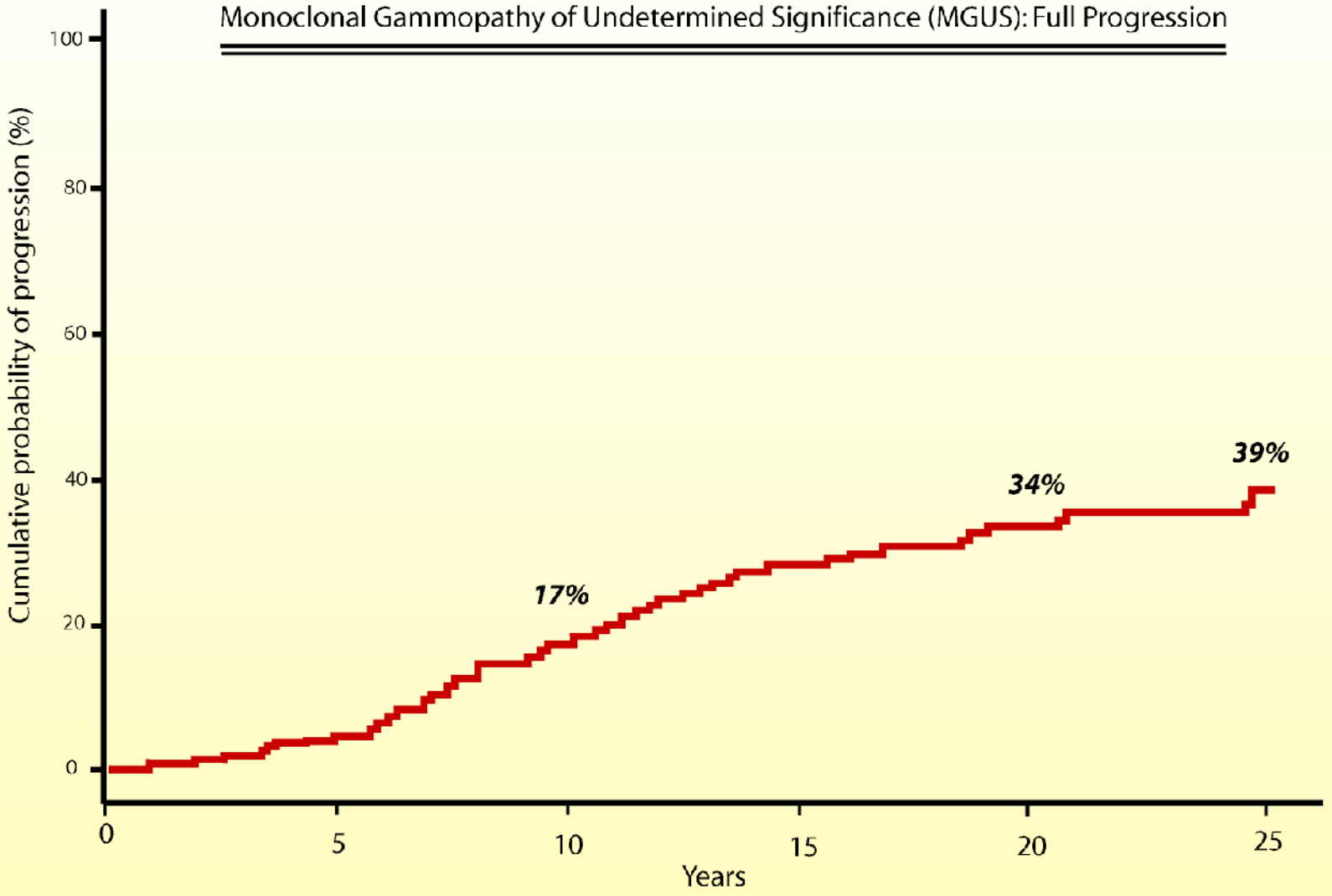
Kyle et al, Mayo Clinic Proceed 79:859, 2004.

MGUS
Development of Myeloma or Related Disease in 64 Patients with MGUS

			Interval to disease (yr)	
	No.	%	Median	Range
Multiple myeloma	44*	69	10.6	1-32
Macroglobulinemia	7	11	10.3	4-16
Amyloidosis	8	12	9.0	6-19
Lymphoproliferative disease	5	8	8.0	4-19
Total	64	100	10.4	1-32

*Dx of myeloma made after 20-yr F-U in 10 pt

Kyle et al, Mayo Clinic Proceed 79:859, 2004.



Mayo Clinic Proceedings 2004; 79:859, Kyle et al.

Conclusion

All patients with an apparently benign monoclonal gammopathy must be followed indefinitely

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

Duration of Follow-up

Person Years	11,009
Range years	0-35
Median years	15.4
Deaths (70%)	963

MGUS
SE MINNESOTA

Relative Risk of Progression

	Obs	Exp*	RR
Multiple Myeloma	75	3	25
Lymphoma	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

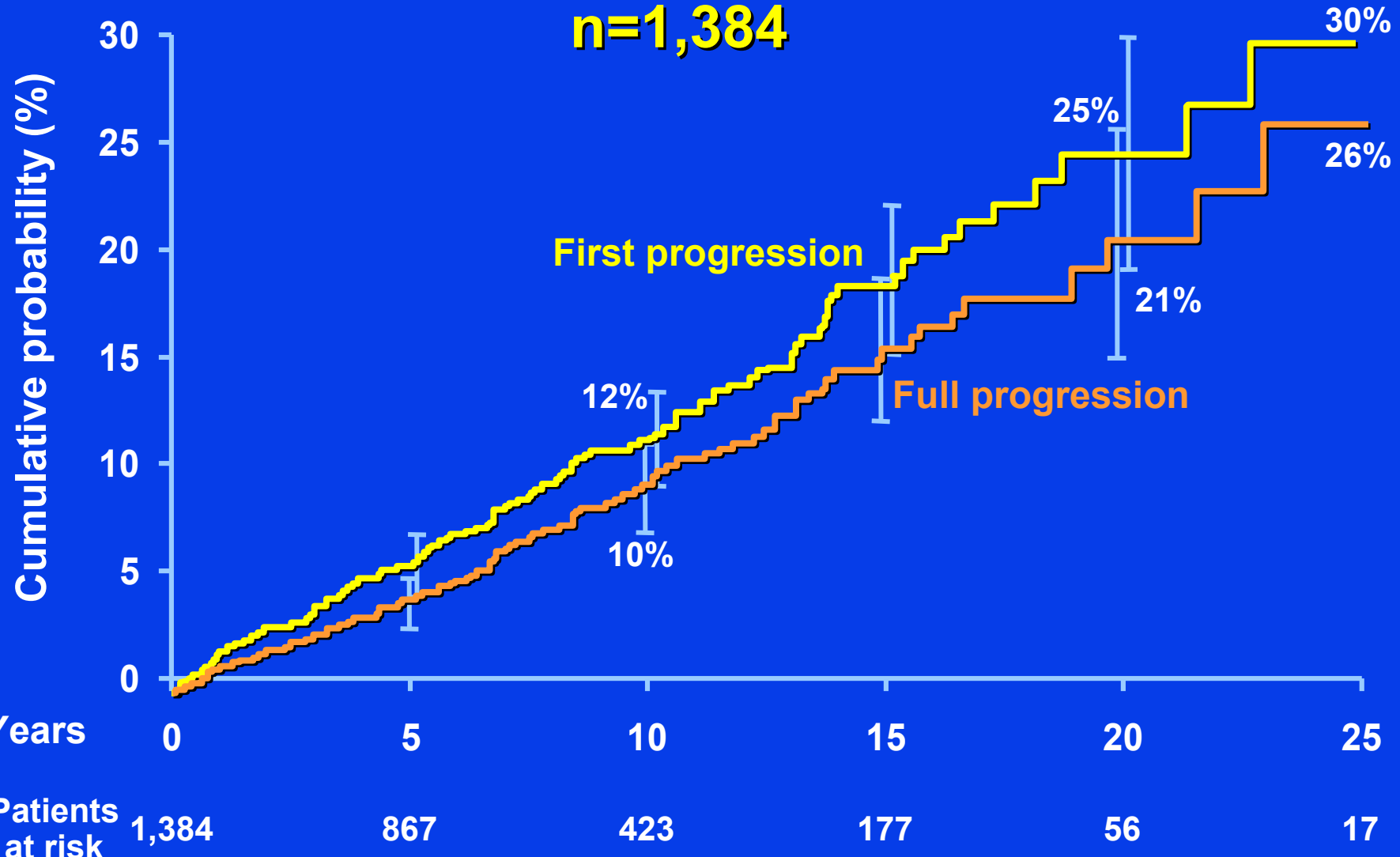
* Iowa SEER Registry

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

MGUS SE Minnesota

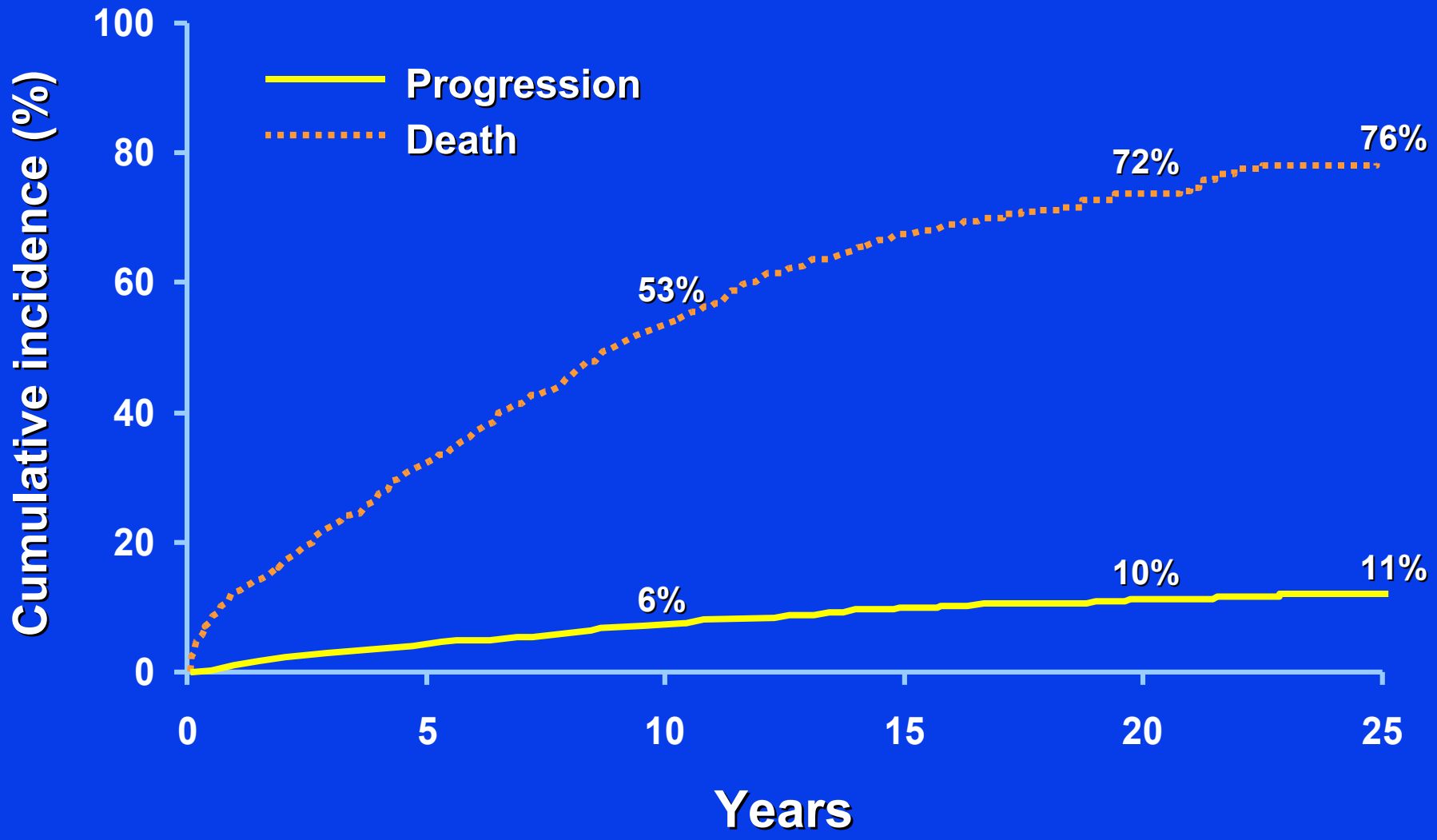
1960-1994

n=1,384



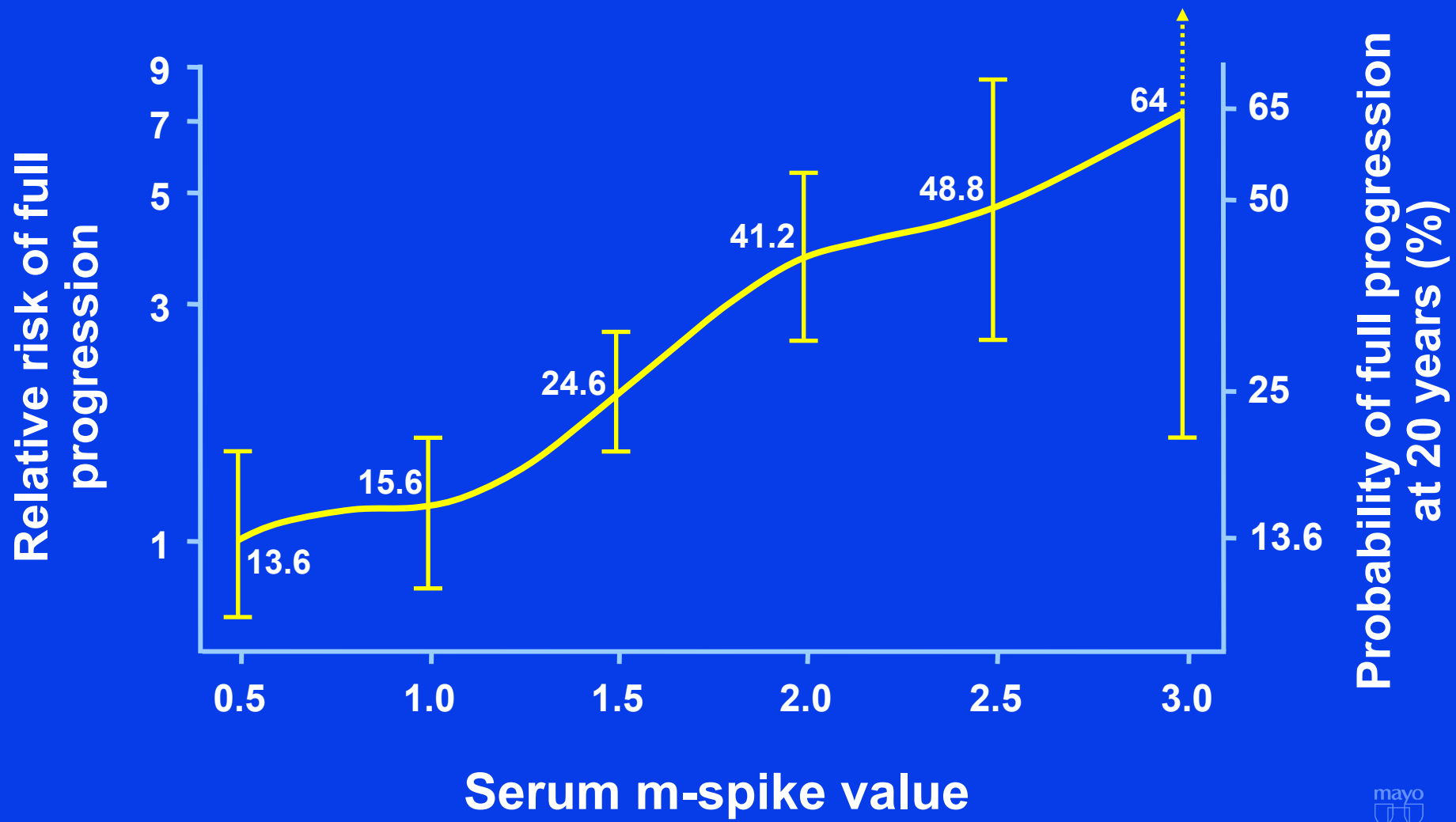
Kyle, et al., New Engl J Med, 346:564,

Full Progression or Death



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

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 95% CI	Risk of Prog 20 yr % Absolute	Risk of Prog 20 yr % 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

MGUS SE Minnesota
Summary

- MGUS patients more likely to die of unrelated disease than to progress
- Myeloma accounts for 65% of progression
- Risk of progression is 1%/year
- Risk of progression associated with size and type of M-protein and FLC

MGUS SE Minnesota Conclusion

All MGUS patients must be monitored forever

Smoldering Multiple Myeloma

- Serum M-spike ≥ 3 g/dl

  and/or

- Bone marrow plasma cells ≥ 10%
- No end organ damage
  - CRAB (hypercalcemia, renal disease, anemia or lytic bone lesions)

Kyle RA and Greipp PR, NEJM, 302:1347, 1980
Kyle et al., NEJM 356:2582, 2007

Smoldering Multiple Myeloma

Mayo Clinic 1970 – 1994

	N	%
Serum M-protein ≥ 3 g/dl and Bone marrow plasma cells ≥ 10%	106	38
Serum M-protein < 3 g/dl and Bone marrow plasma cells ≥ 10%	143	52
Serum M-protein ≥ 3 g/dl and Bone marrow plasma cells < 10%	27	10
TOTAL	276	100

Kyle et al., NEJM 356:2582, 2007

Smoldering Multiple Myeloma

Progression

	N	%	Expected No. Pts	R.R.
Multiple myeloma	157	57	0.3	522
Primary amyloid (AL)	5	2	0.1	50
Total	162	59		

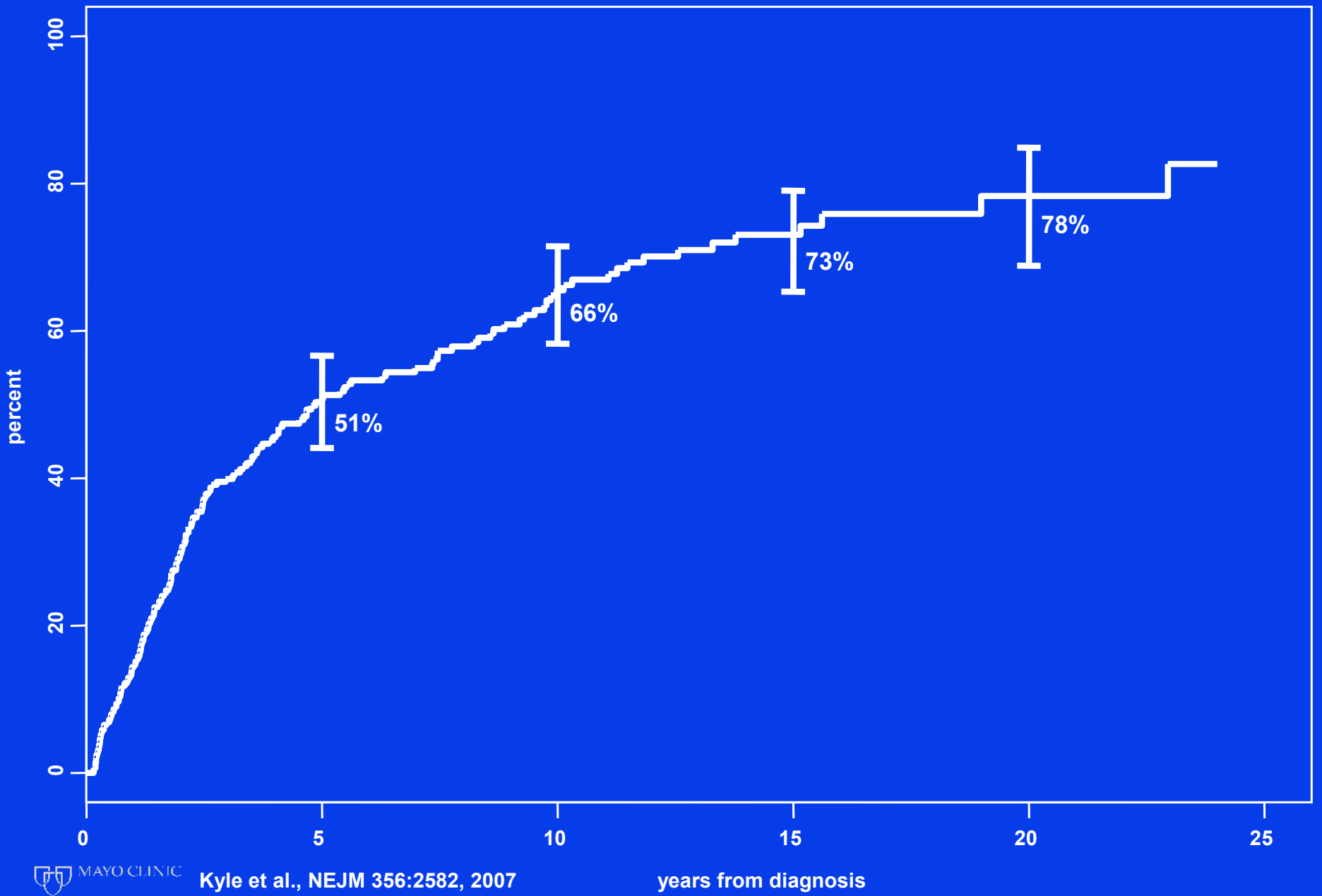
Kyle et al., NEJM 356:2582, 2007

Smoldering Multiple Myeloma

Time to progression	Median years	% progression at 15 years
Serum M-spike ≥ 3 Bone marrow plasma cells ≥ 10	2	87
Serum M-spike < 3 Bone marrow plasma cells ≥ 10	8	70
Serum M-spike ≥ 3 Bone marrow plasma cells < 10	19	39
Total (N = 276) p= <0.001	5	73

Kyle et al., NEJM 356:2582, 2007

Progression to Multiple Myeloma or Amyloid



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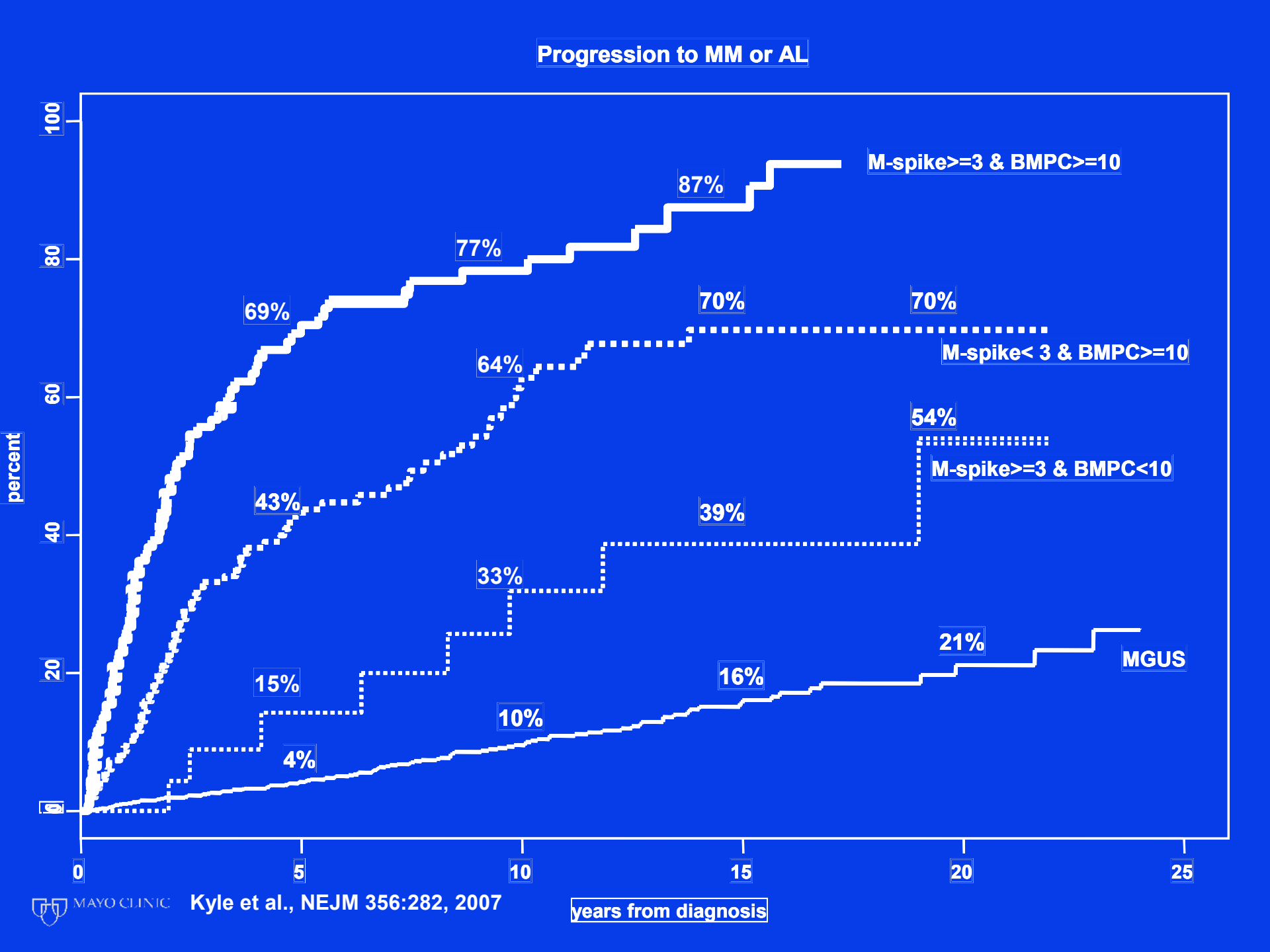
Kyle et al., NEJM 356:2582, 2007

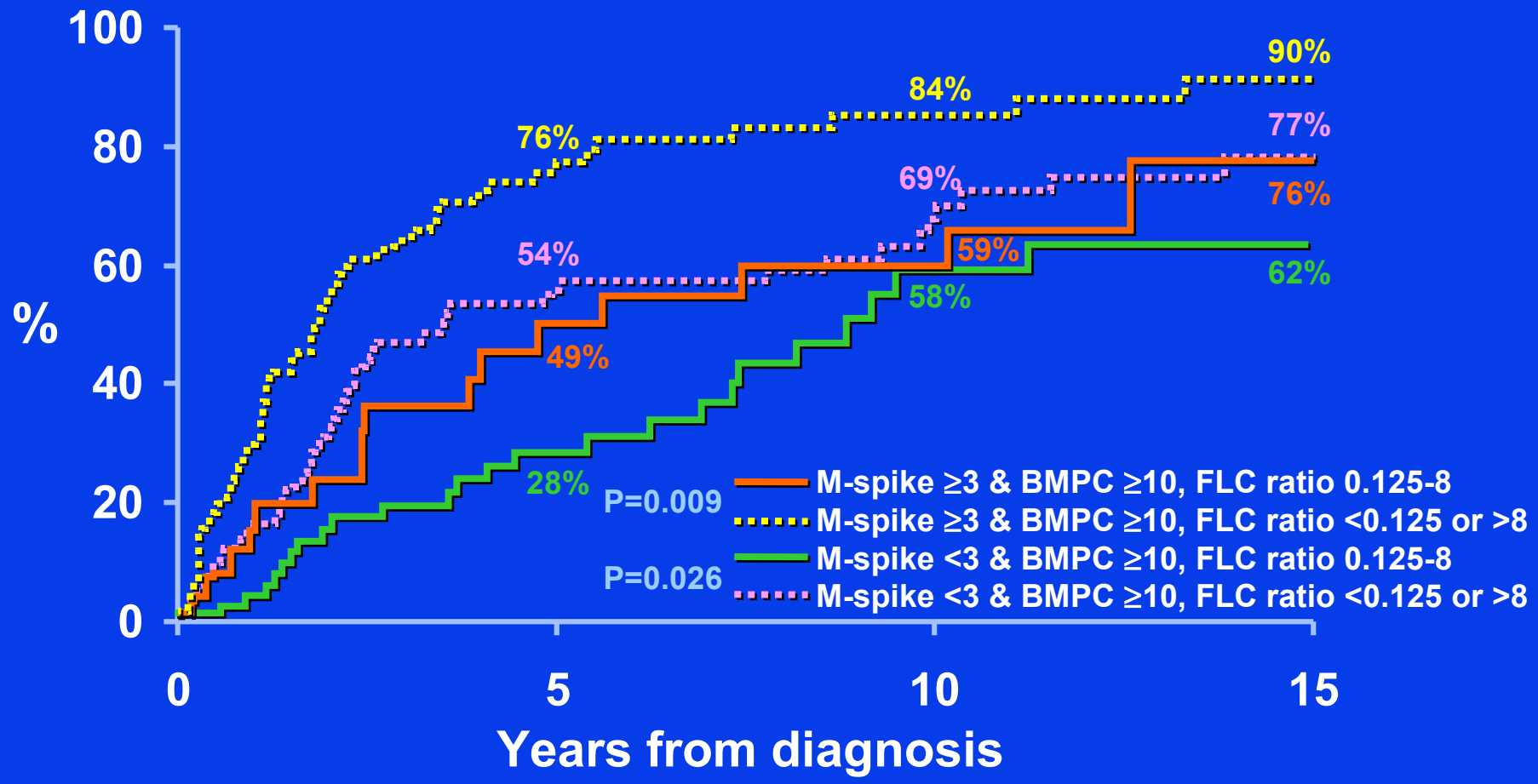

Progression to MM or AL
M-spike>=3 & BMPC>=10
87%
77%
69%
70%
70%
M-spike< 3 & BMPC>=10
64%
54%
M-spike>=3 & BMPC<10
43%
39%
33%
21%
MGUS
16%
15%
10%
4%
100
80
60
40
20
0
percent
0
5
10
15
20
25
years from diagnosis
MAYO CLINIC
Kyle et al., NEJM 356:282, 2007

Smoldering Multiple Myeloma
Role of Free Light Chain (FLC)

	N	Relative Risk
Serum M protein ≥ 3 g/dL & BMPC ≥ 10%		
FLC ratio < 0.125 or > 8	78	2.06
Serum M protein < 3 g/dL & BMPC ≥ 10%		
FLC ratio < 0.125 or > 8	82	1.72

Dispenzieri et al: Blood 111:785, 2008

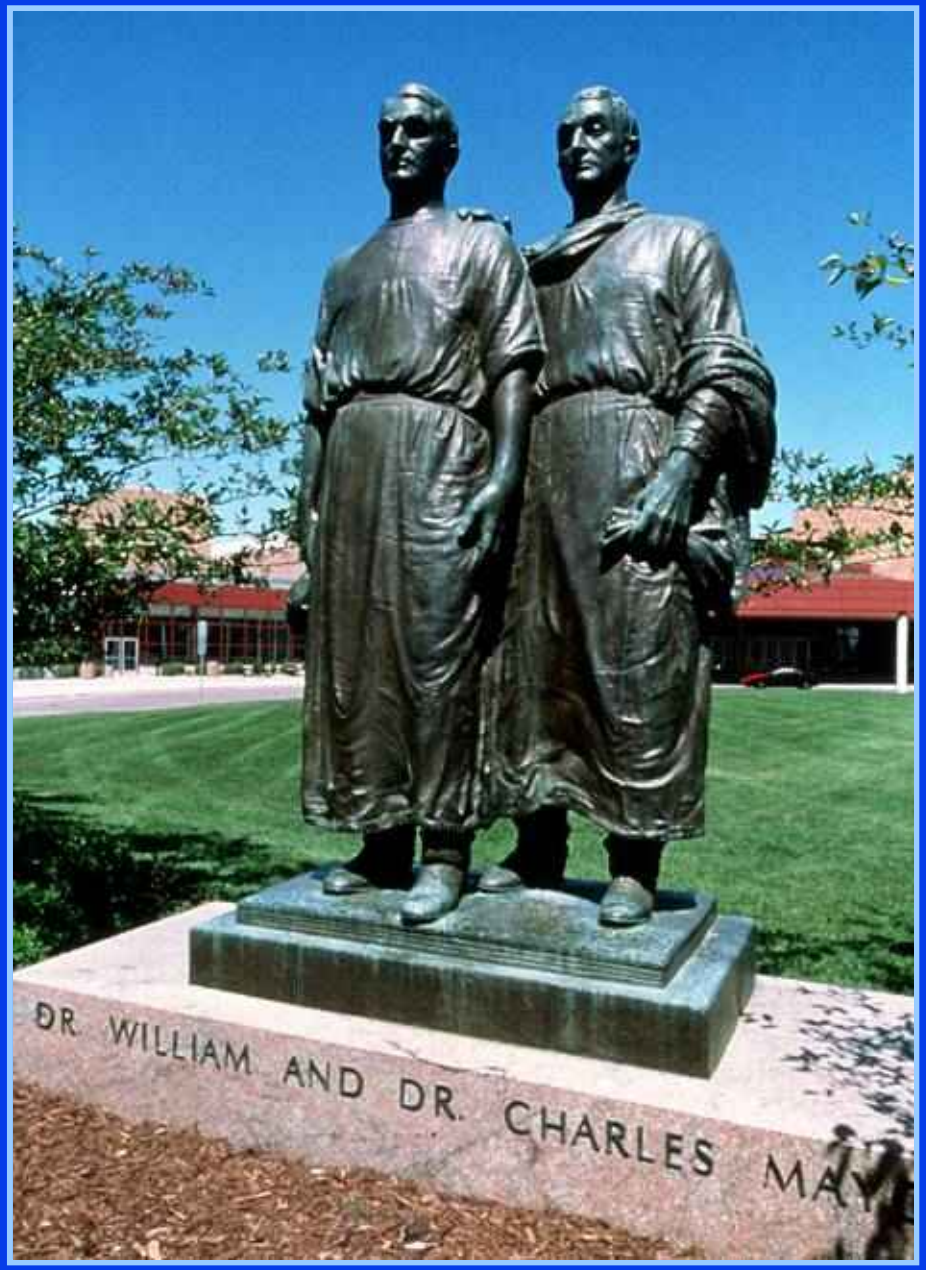
Smoldering Multiple Myeloma
Progression to MM or AL



Dispenzieri et al: Blood 111:785, 2008

“It is important to realize that everything discovered in a particular field is almost nothing in comparison with what remains to be discovered.”

Santiago Ramón y Cajal


DR. WILLIAM AND DR. CHARLES MAY