Clonal evolution in MGUS

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Monoclonal plasma cell disorders: a dynamic spectrum

MGUS → **Smoldering multiple myeloma** → **Symptomatic myeloma**

Increasing levels of monoclonal protein →

Increasing marrow plasma cell percentage →

Development of CRAB features →

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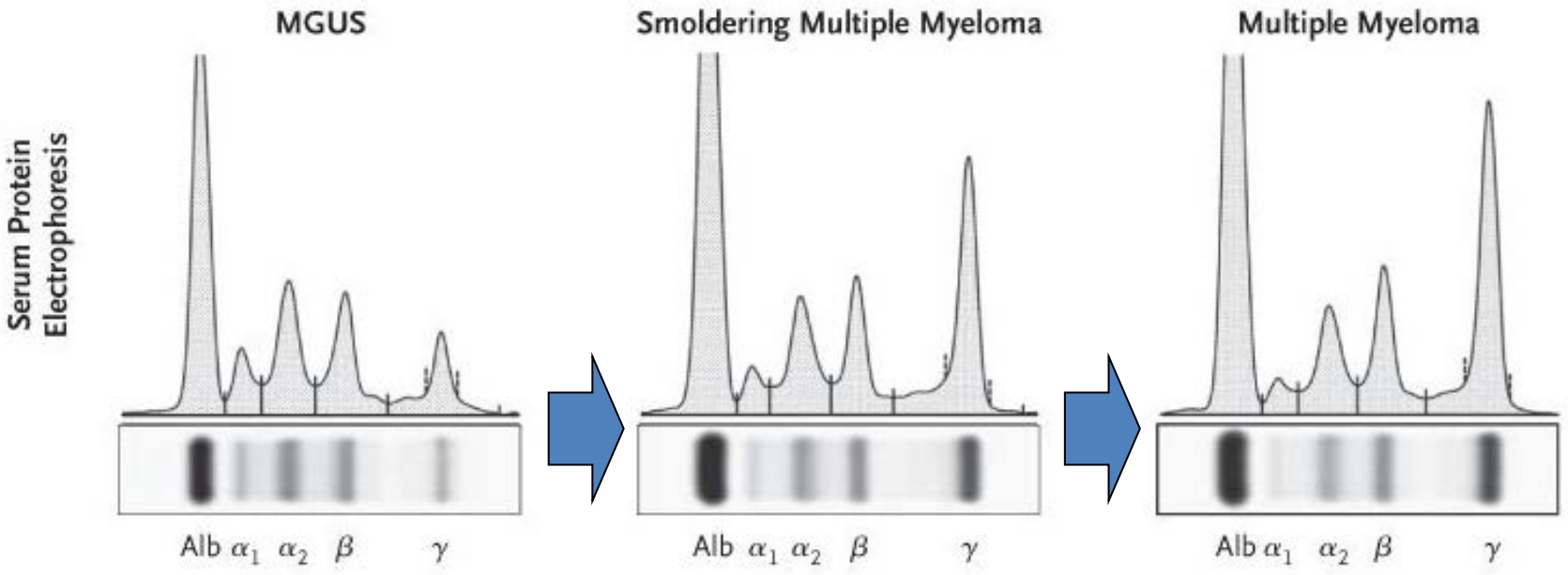
Spectrum of monoclonal gammopathies



M spike < 3 g/dL

BMPC% < 10%

No CRAB

M spike ≥ 3 g/dL

BMPC% ≥ 10%

No CRAB

CRAB

Needs treatment

Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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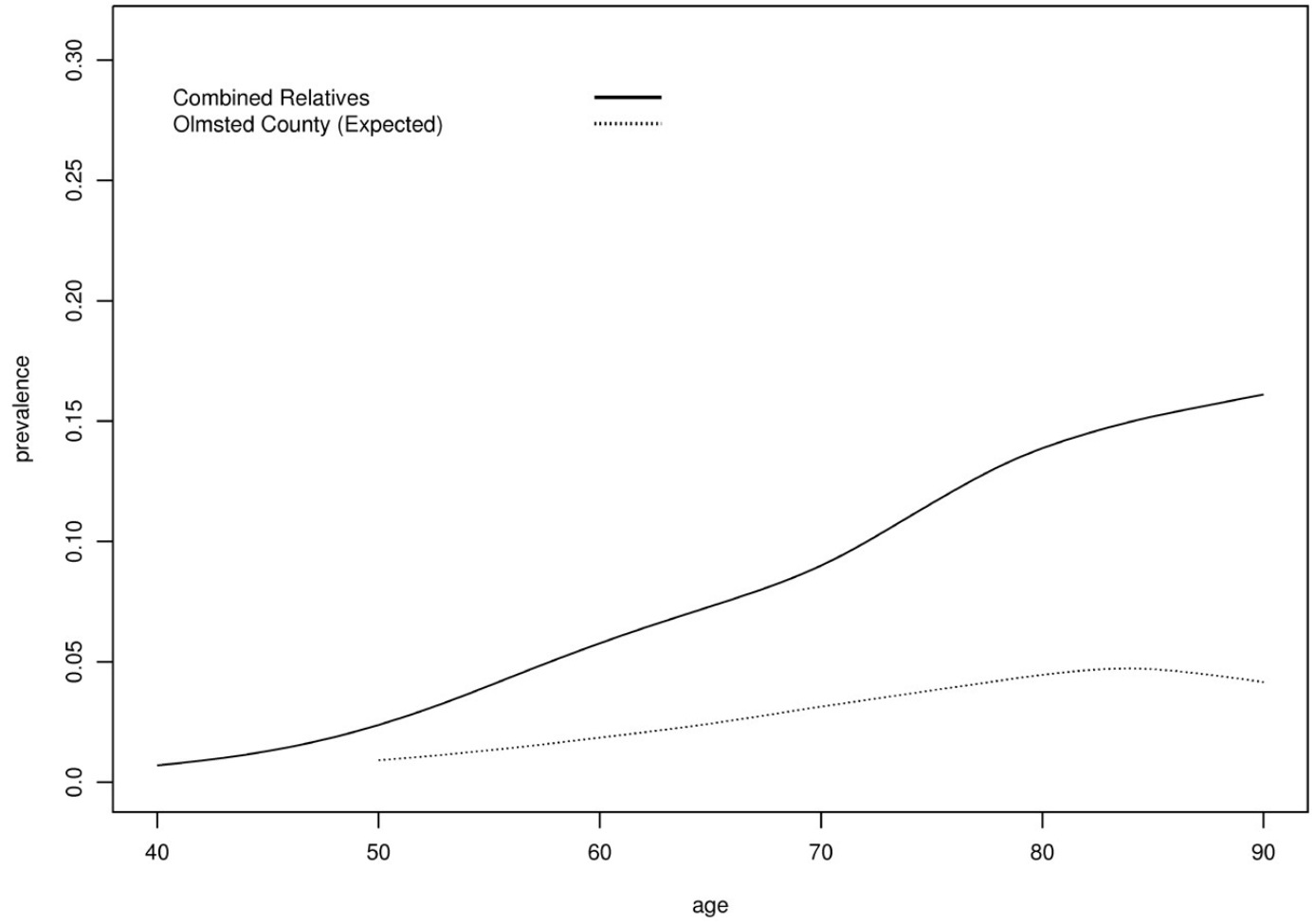
Risk factors for plasma cell disorders

- Race: Higher risk in African Americans
  - Similar risk in a population from Ghana
- Chemical and radiation exposure
  - Increased risk among those with pesticide exposure
- Familial risk
  - Increased risk among first degree relatives

MGUS prevalence for first-degree relatives of MM or MGUS



Vachon C M et al. Blood 2009;114:785-790

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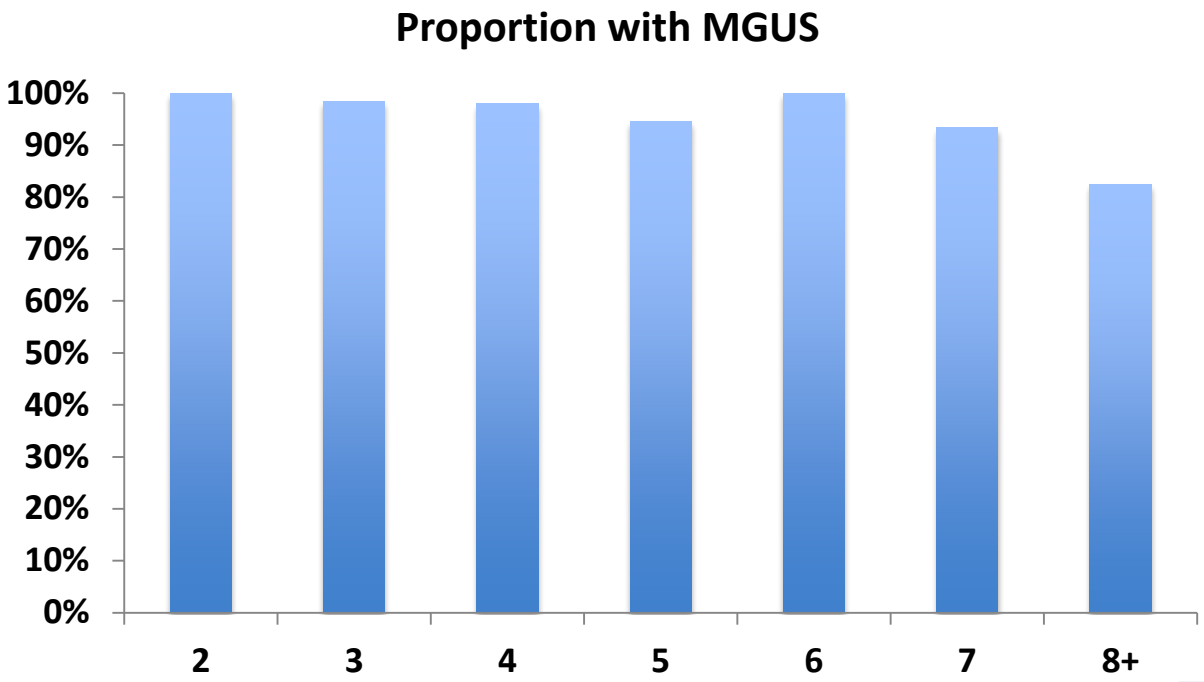
MGUS is a true “pre-cancerous” state

- MM is always preceded by MGUS stage
- Among 77 469 healthy adults from PLCO Cancer Screening Trial: 71 subjects developed MM



Landgren O, Blood. 2009 :5412-7.

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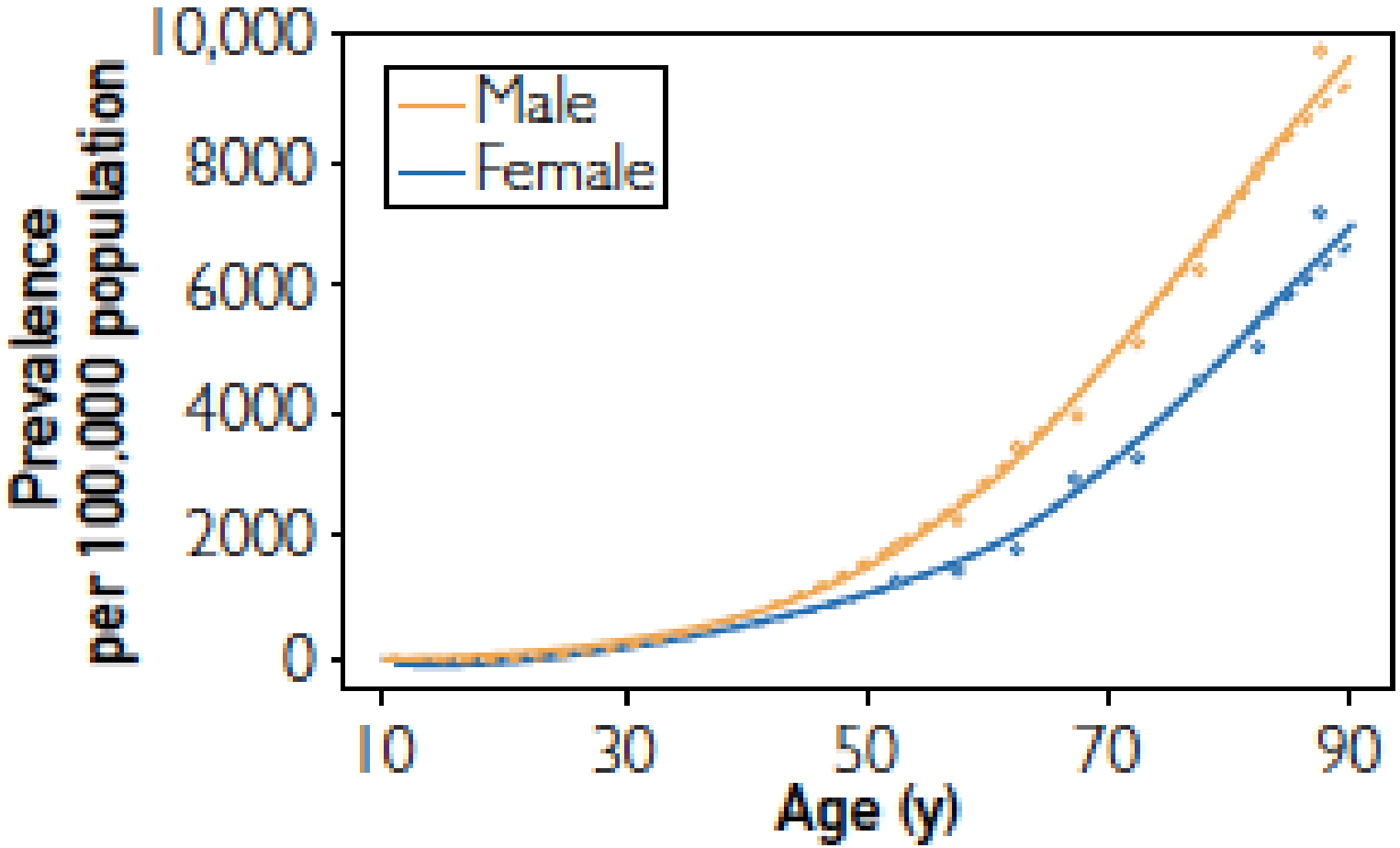
MGUS starts early



Therneau, T. M., et al. (2012) Mayo Clin Proc 87(11): 1071-1079.

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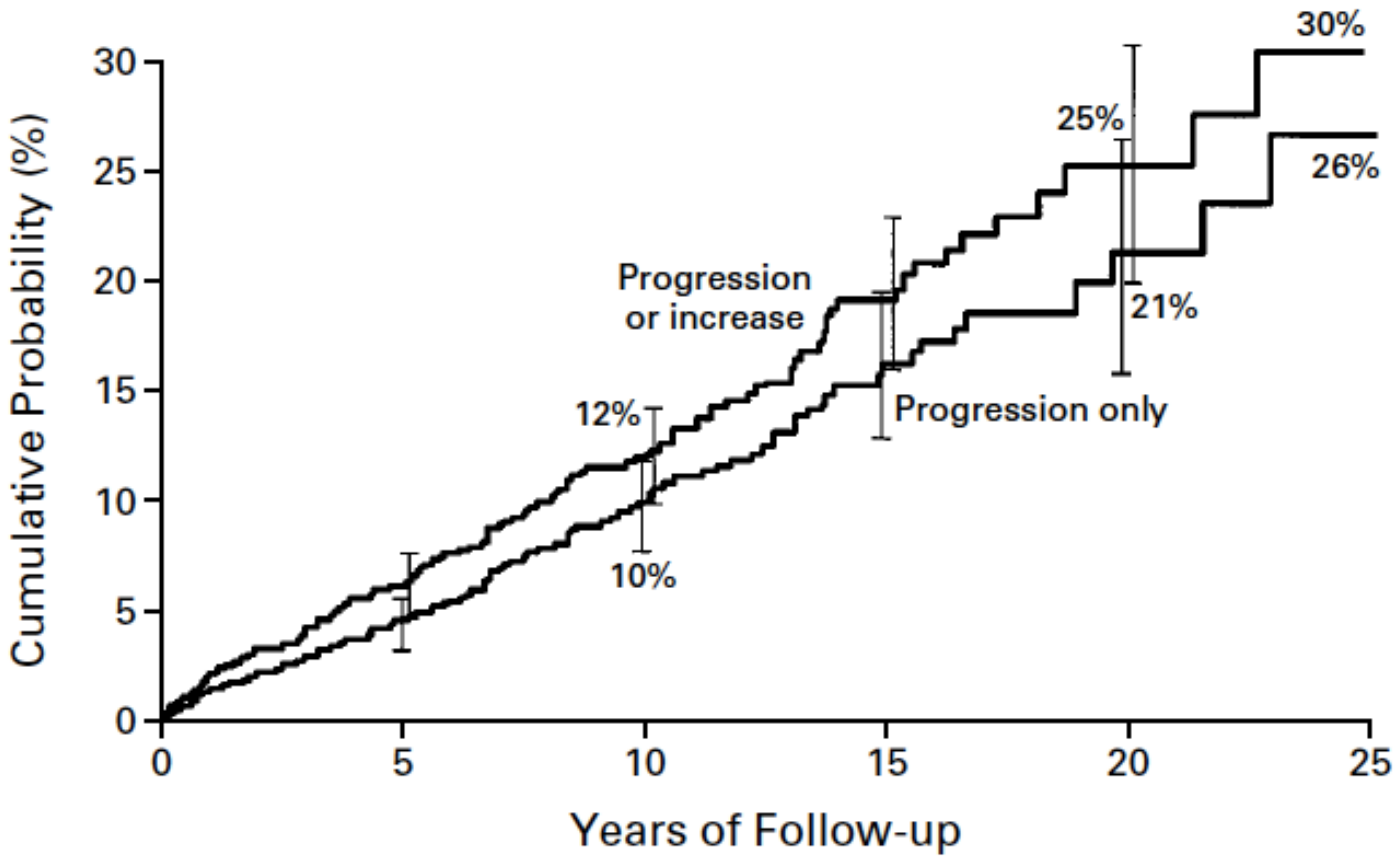
MGUS risk of progression



Kyle et al, N Engl J Med 2002; 346:564-569

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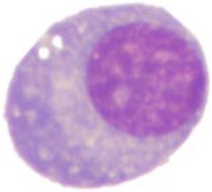
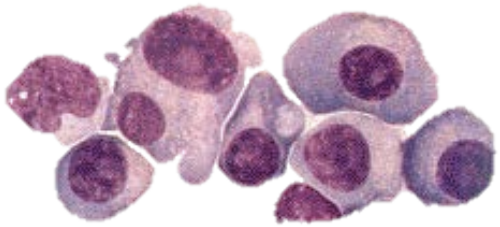
Clonal Evolution Paradigm

Evolution of the clonal plasma cell

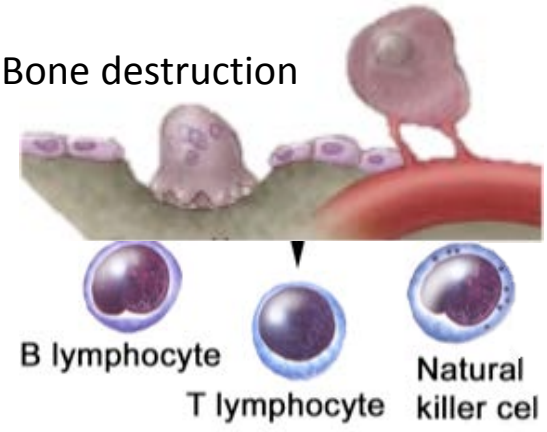




Alteration of the marrow and extramedullary microenvironment

Angiogenesis

Bone destruction



Immune alteration

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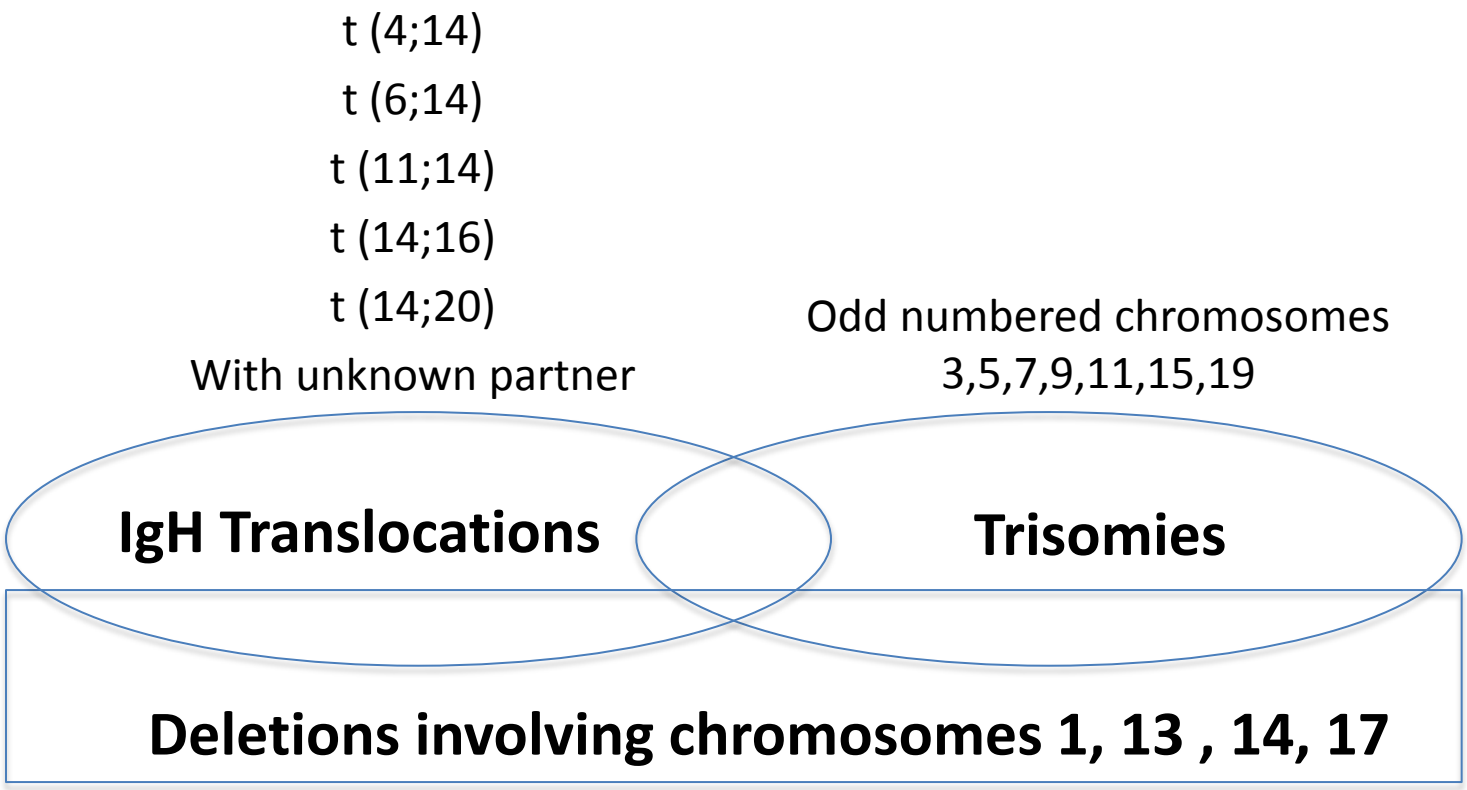
The malignant clonal PC

Hyperplastic polyp → **Tubular adenoma** → **Villous adenoma** → **Adenocarcinoma**

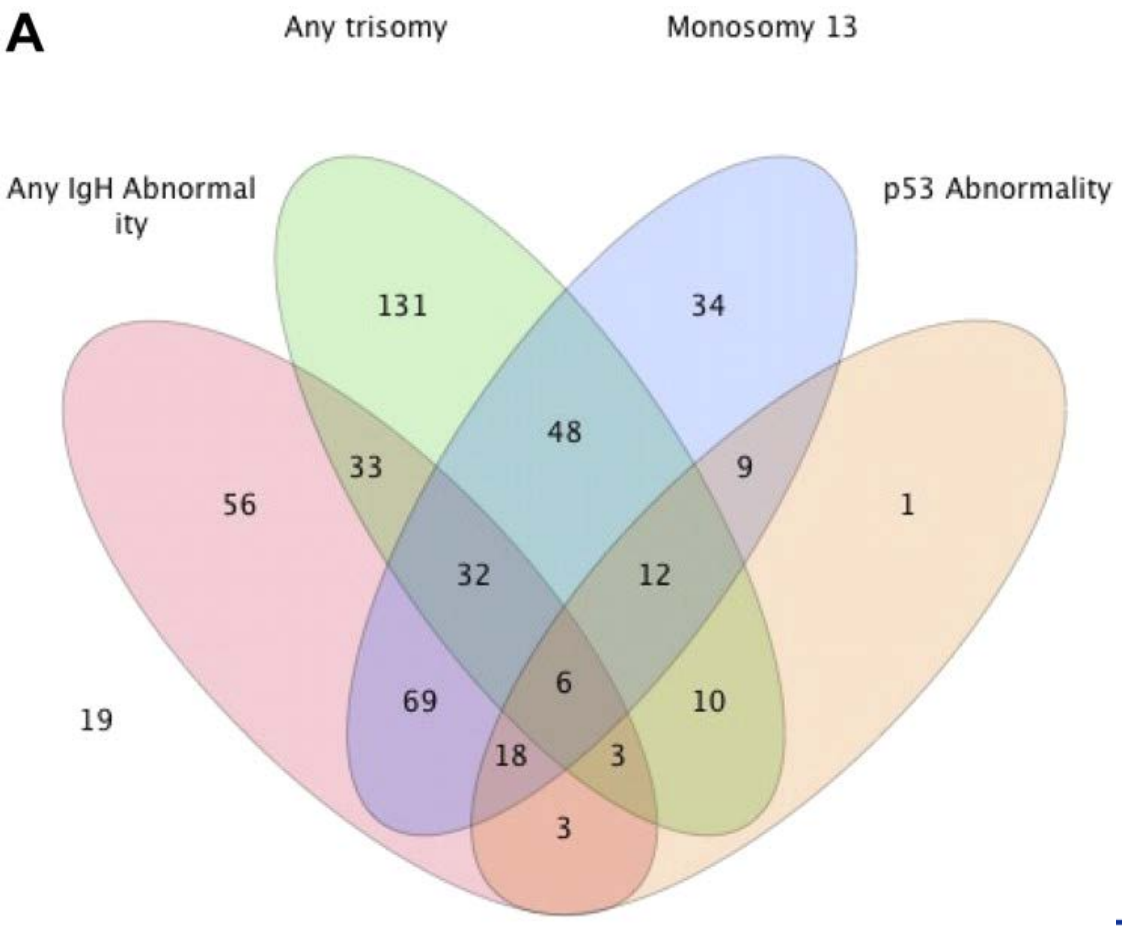
But…..morphology inadequate to differentiate the ‘malignant’ clonal plasma cell ☹

FISH abnormalities in PCD



Kumar S, *Blood*. 2012;119(9):2100-2105

FISH abnormalities in MM



Kumar S, *Blood*. 2012;119(9):2100-2105

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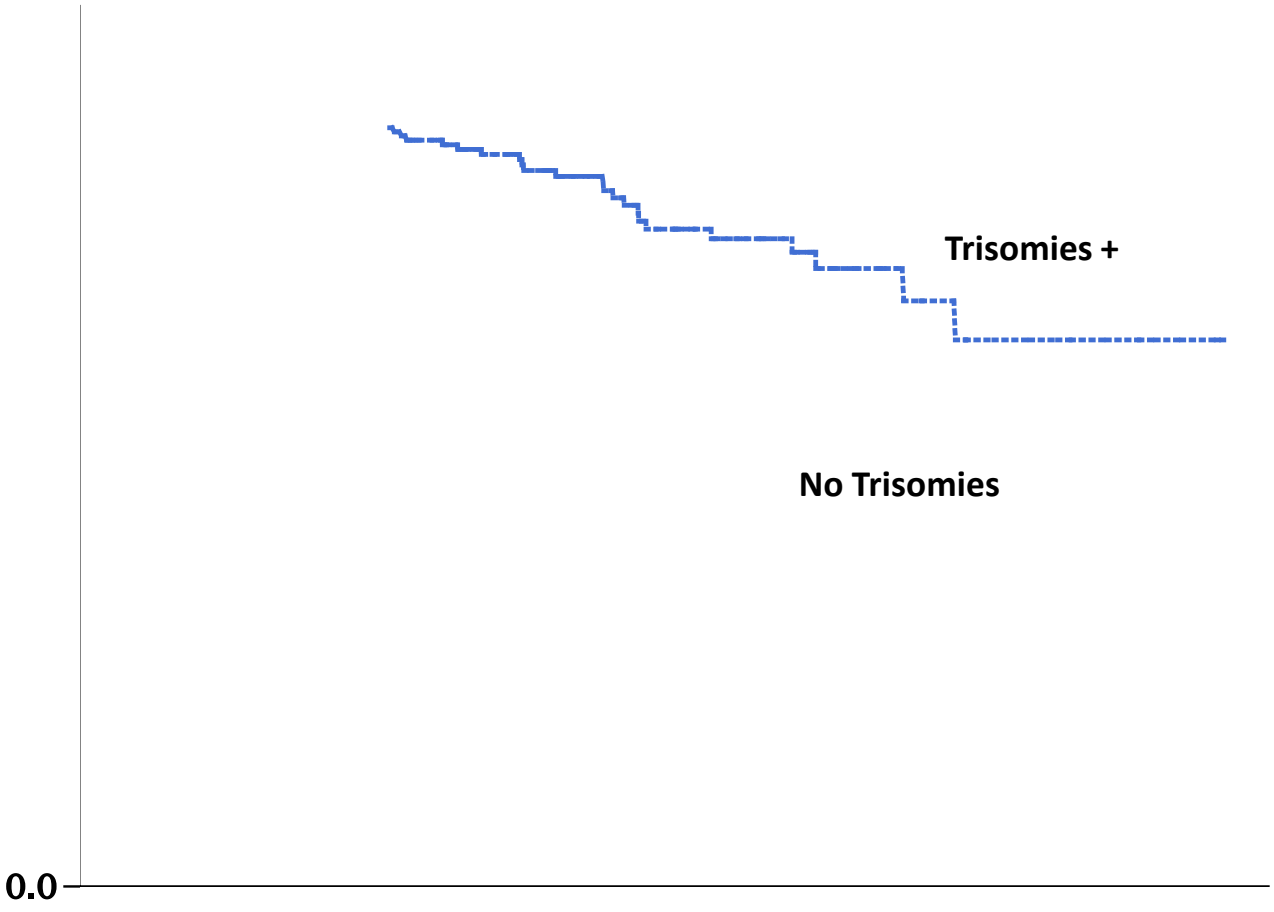
Trisomies and outcome in myeloma



Kumar S, *Blood*. 2012;119(9):2100-2105

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FISH abnormalities in MM and SMM

FISH abnormality	Frequency (%)	
	SMM (N=351)	MM (N=484)
Trisomy (ies) without IgH abnormality	*154 (44%)*	*201 (42%)*
IgH abnormality without trisomy (ies)	*127 (36%)*	*146 (30%)*
IgH abnormality with Trisomy (ies)	*14 (4%)*	*74 (15%)*
Other cytogenetic abnormalities	*3 (1%)*	*48 (10%)*
Normal / insufficient	*53 (16%)*	*15 (3%)*

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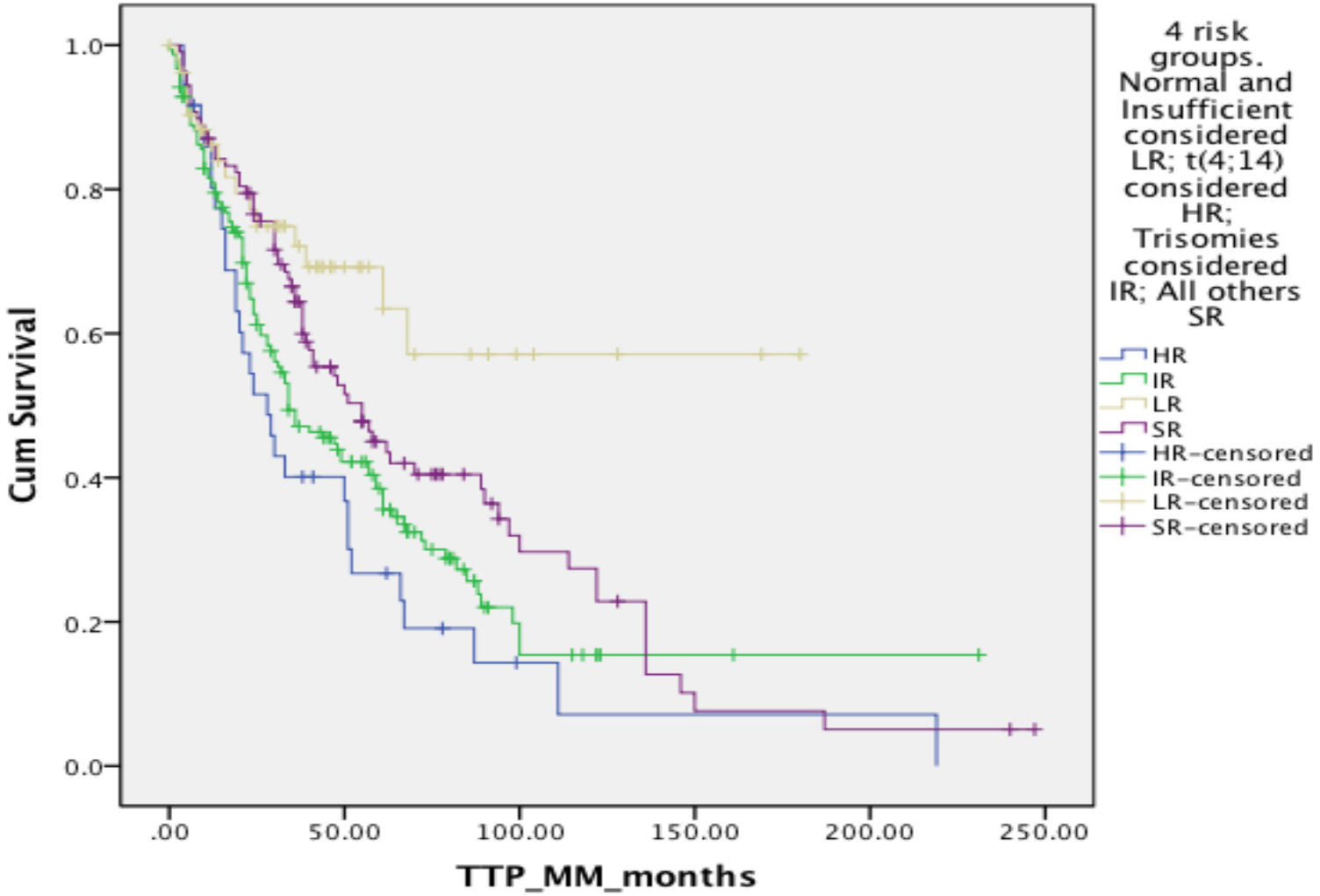
Rajkumar et al, *Leukemia*. March 2013 (epub); Kumar S, *Blood*. 2012;119(9):2100-2105

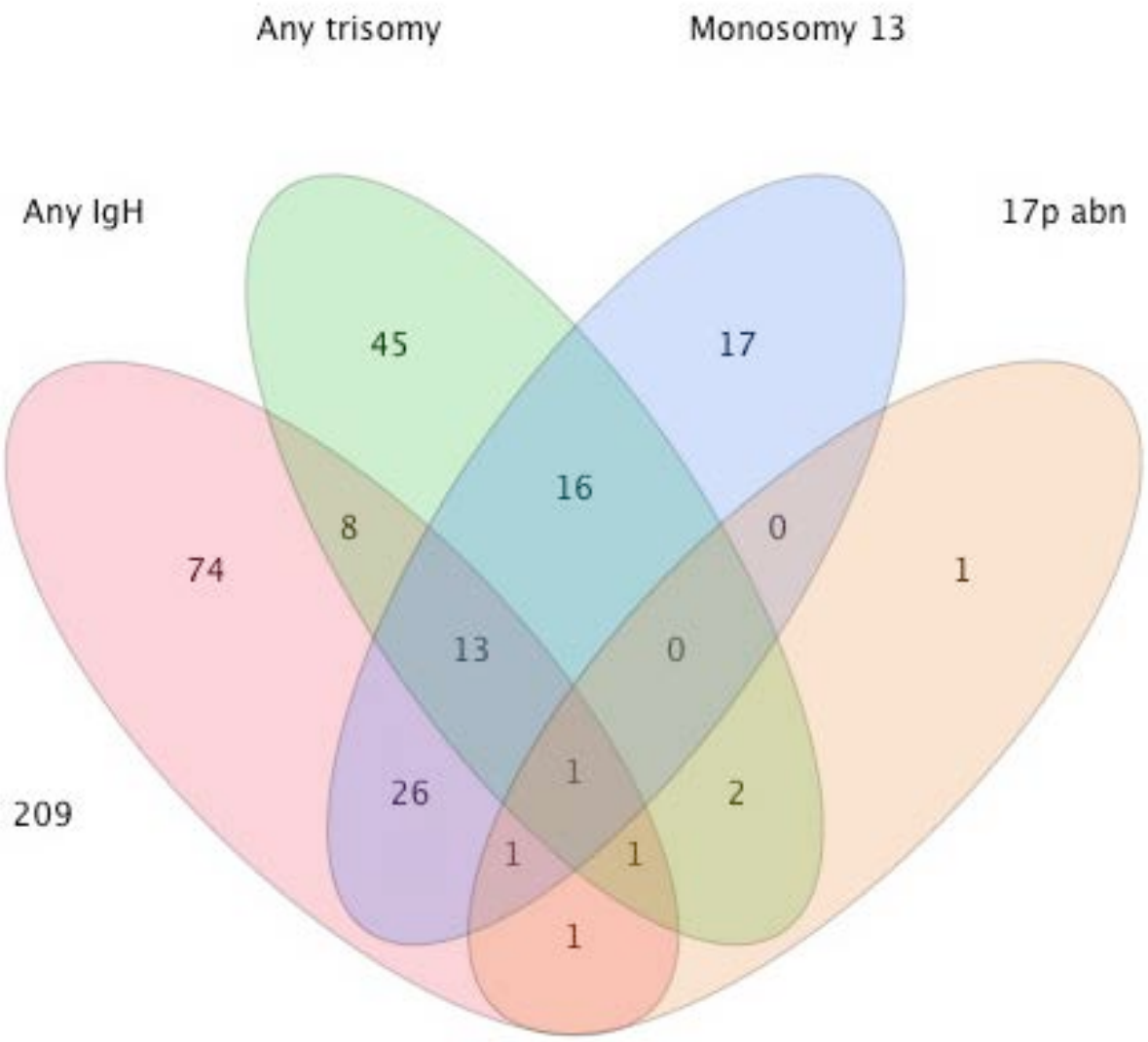
Genetic abnormalities and risk of progression in SMM



MAYO CLINIC

Rajkumar et al, *Leukemia*. March 2013 (epub)

FISH abnormalities in MGUS



Kumar et al, *unpublished data*

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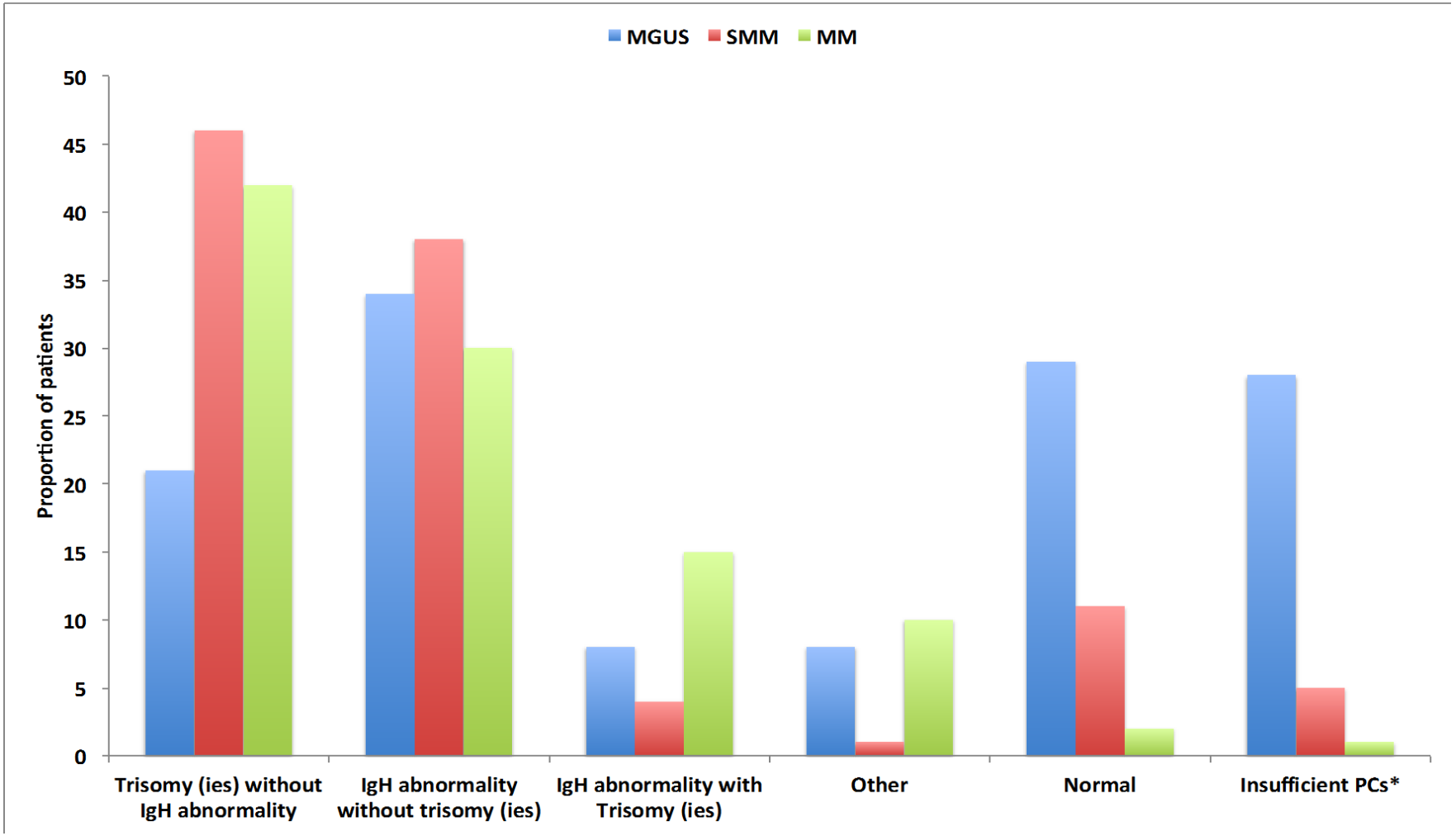
FISH evolution in plasma cell disorders



* As a proportion of all patients, others as a proportion of FISH with adequate PCs

Kumar et al, *unpublished data*

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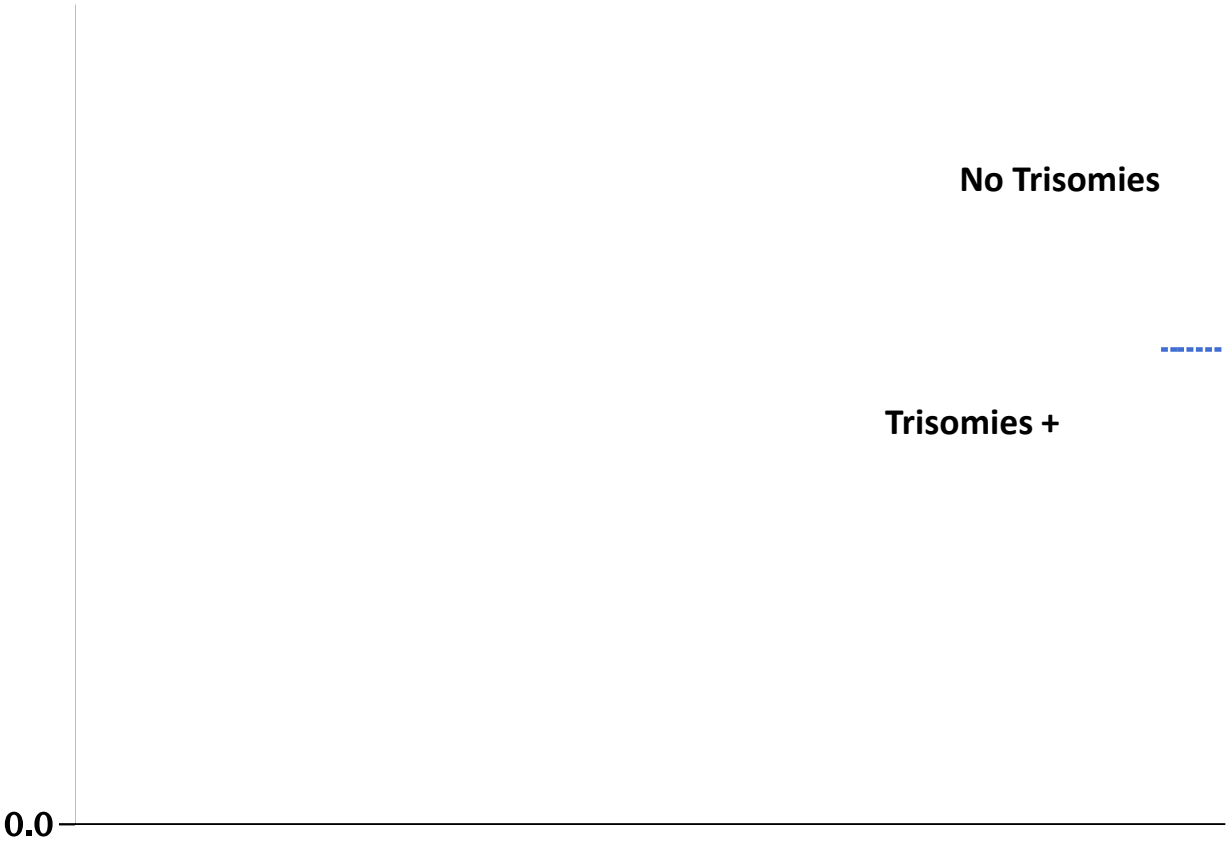
Trisomies and risk of progression in MGUS



Kumar et al, *unpublished data*

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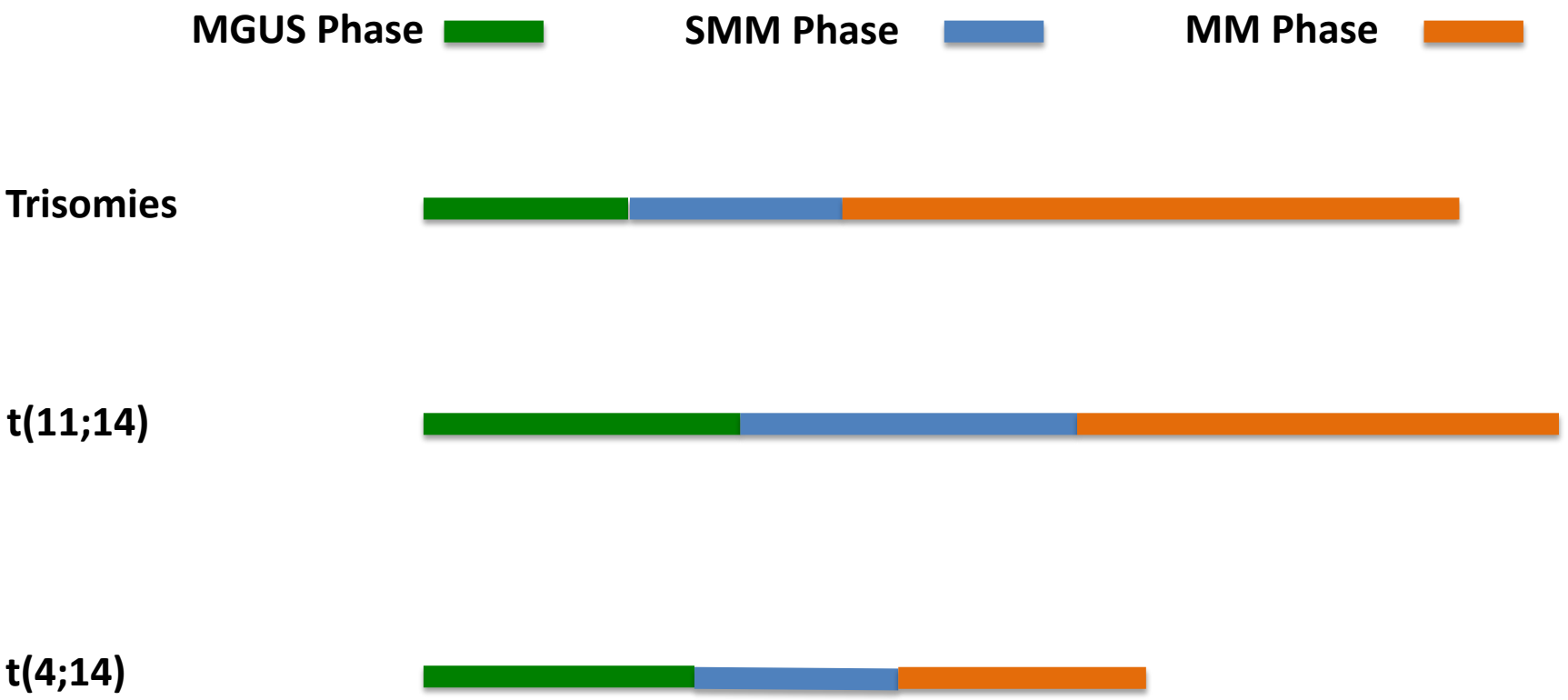
Phenotypic classification and genetic type



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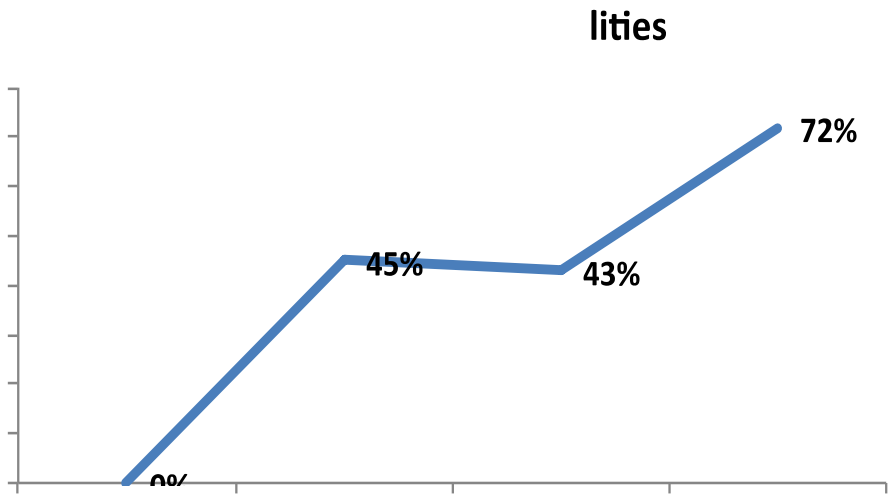
CKS1 amplification

	n	BM PCs (median %)	CKS1B AMP
MGUS	24	4·5 (3–8)	0/23 (0%)
MM at diagnosis	50	62 (15–95)	18/50 (36%)
MM at relapse	25	60 (20–100)	13/25 (52%)
PCL	26	80 (20–100)	16/26 (62%)



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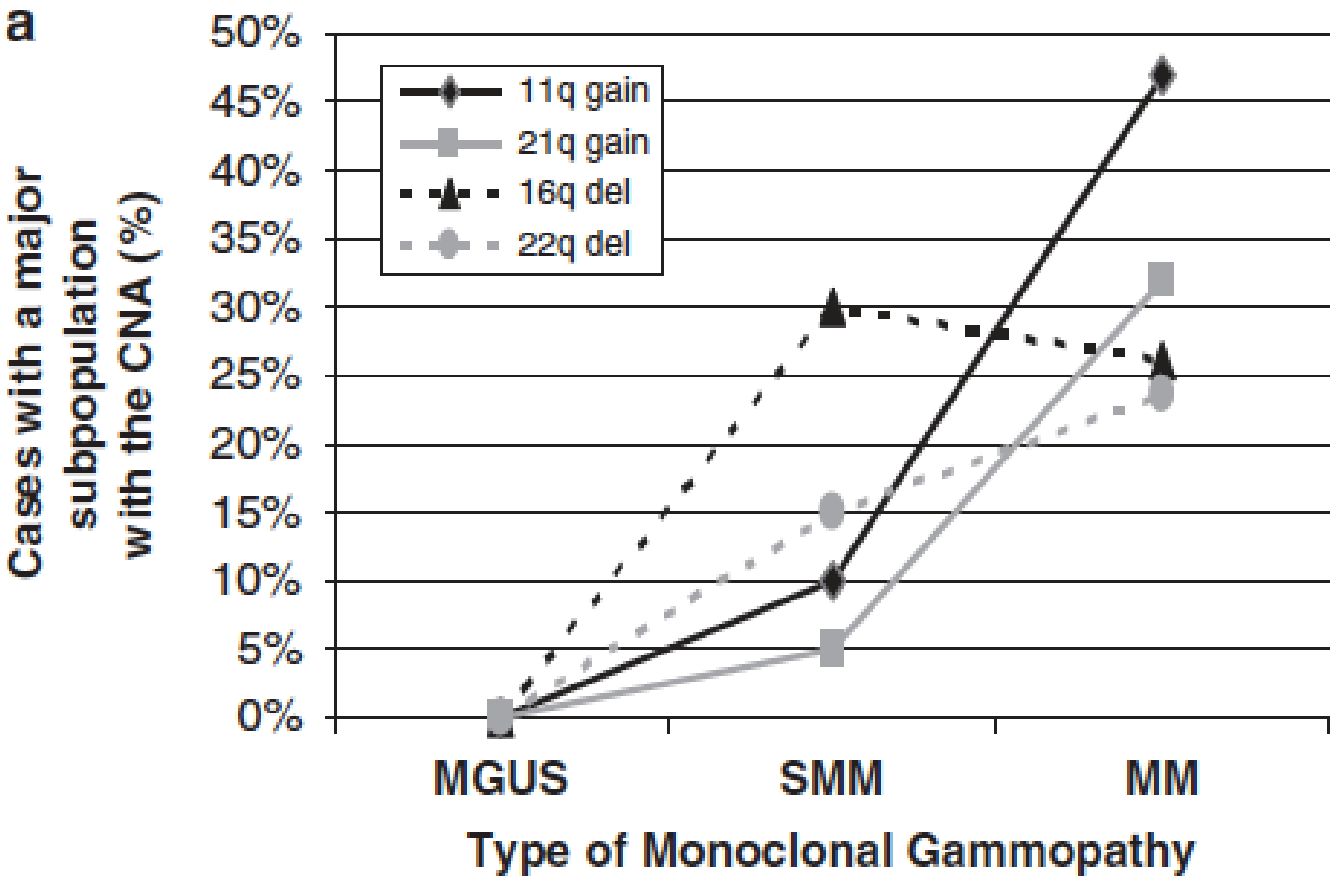
Chang, H., et al. (2006). Br J Haematol 134(6): 613-615; Hanamura, I., et al. (2006). Blood 108(5): 1724-1732.

Copy number abnormalities



Lopez-Corral, L., et al. (2012). Leukemia 26(12): 2521-2529.

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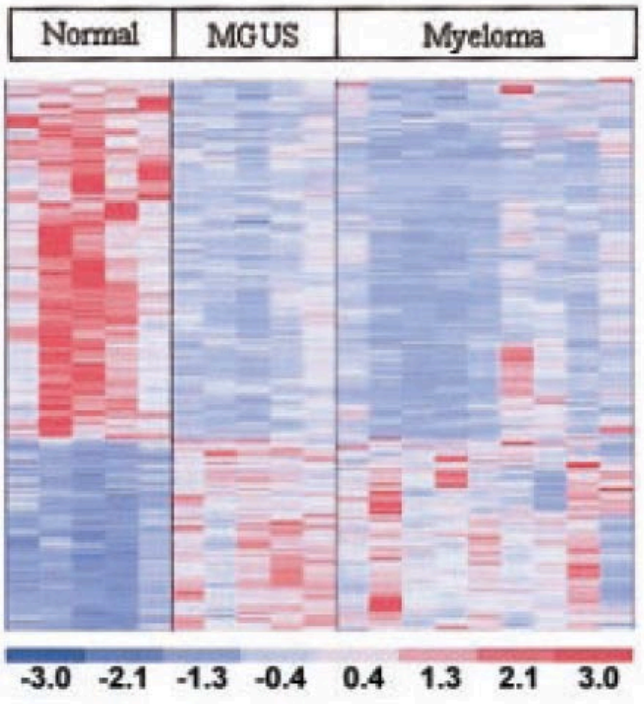
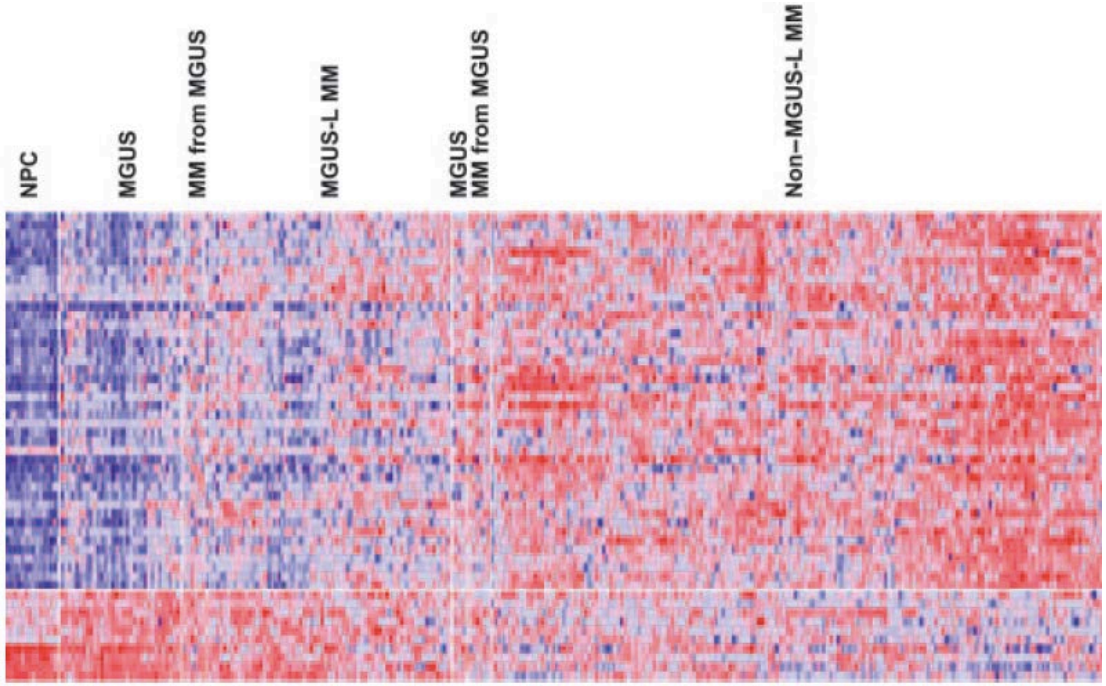
Gene expression changes





Davies, F. E., et al. (2003). Blood 102(13): 4504-4511.

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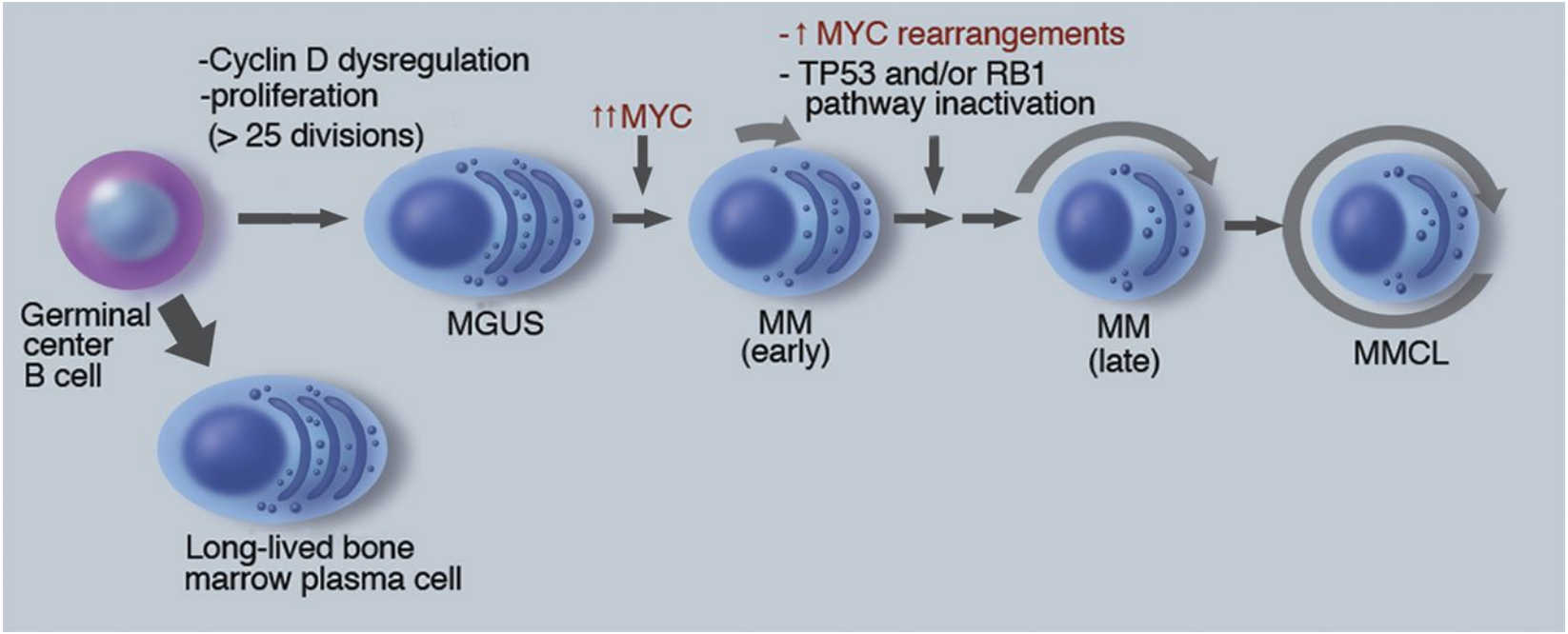
The role of MYC



Kuehl W M , and Bergsagel P L Blood 2012;120:2351-2352

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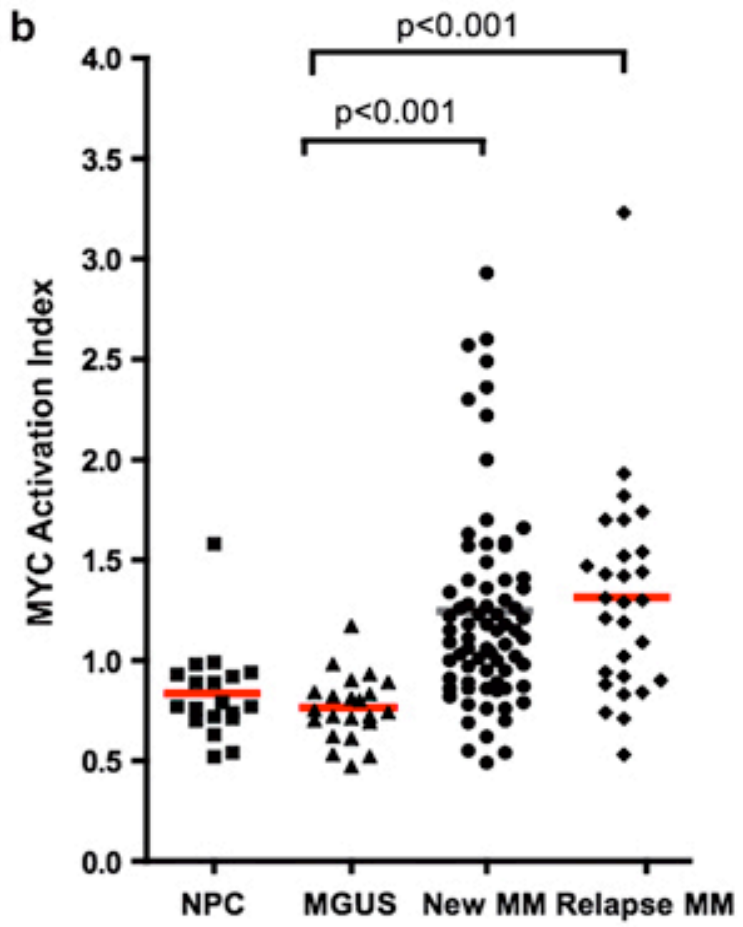
Myc as a marker of malignant progression



Chng et al Leukemia 2011

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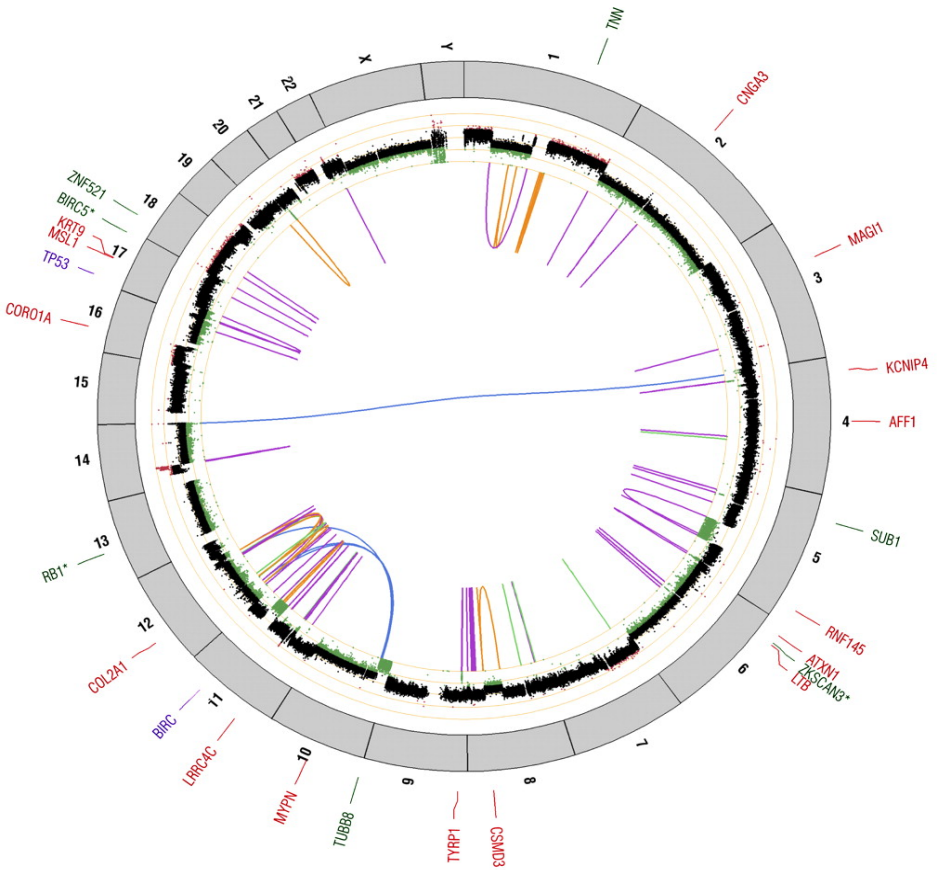
Malignant PC = unstable genome



Innermost line plots:

- Translocation
- Read pairs direction facing each other
- Read pairs facing the same direction
- Read pairs facing in opposite directions

Middle array CGH plot:

- Amplification
- Deletion

Outermost gene labels:

- Deleted genes
- SNV shared with all tumor time points
- SNV unique to sPCL
- * Truncating SNV

Egan J B et al. Blood 2012;120:1060-1066

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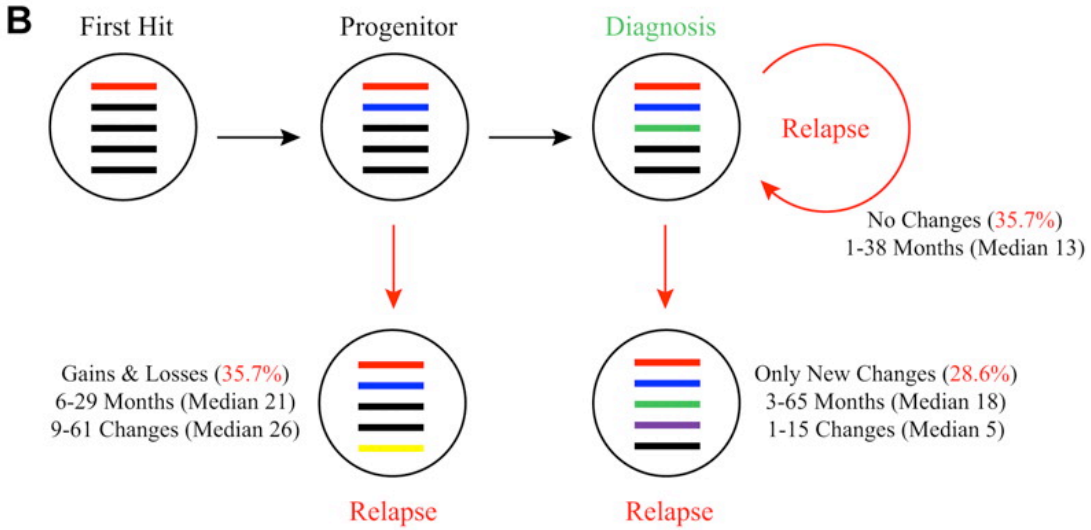
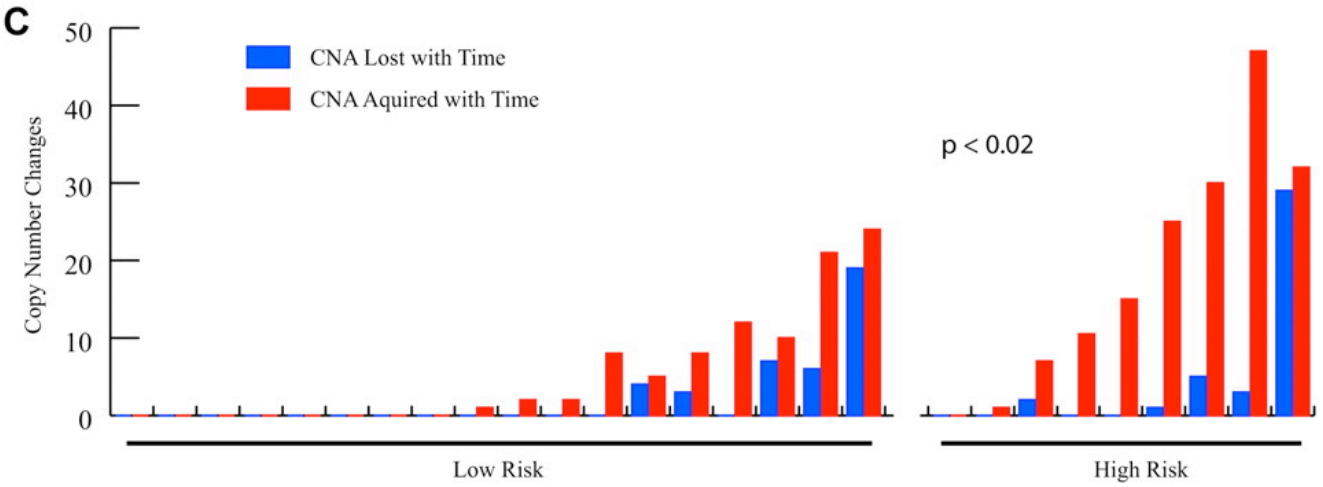
Patterns of clonal evolution in MM





Keats J J et al. Blood 2012;120:1067-1076

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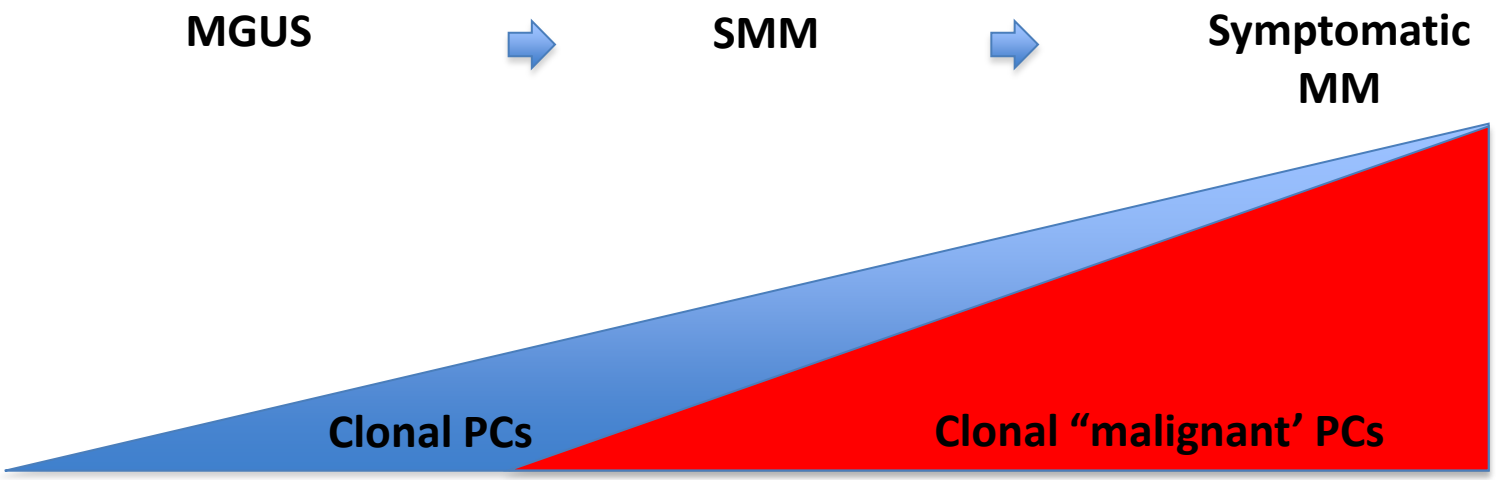
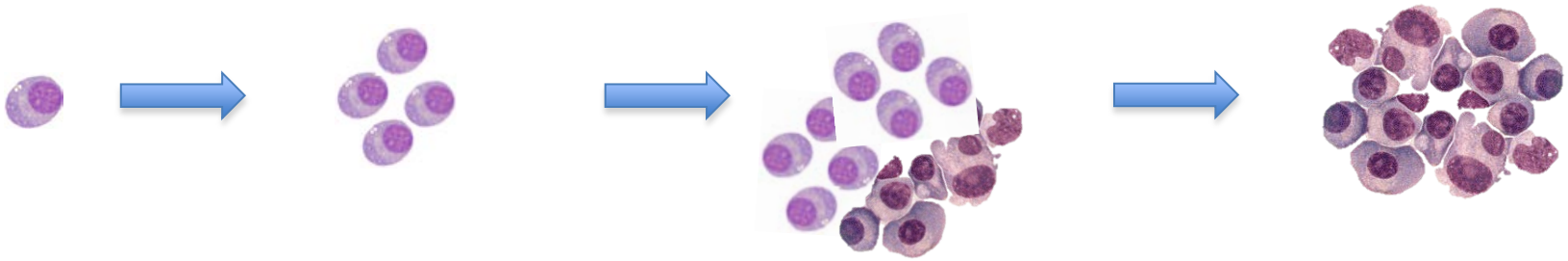
The evolution of MGUS





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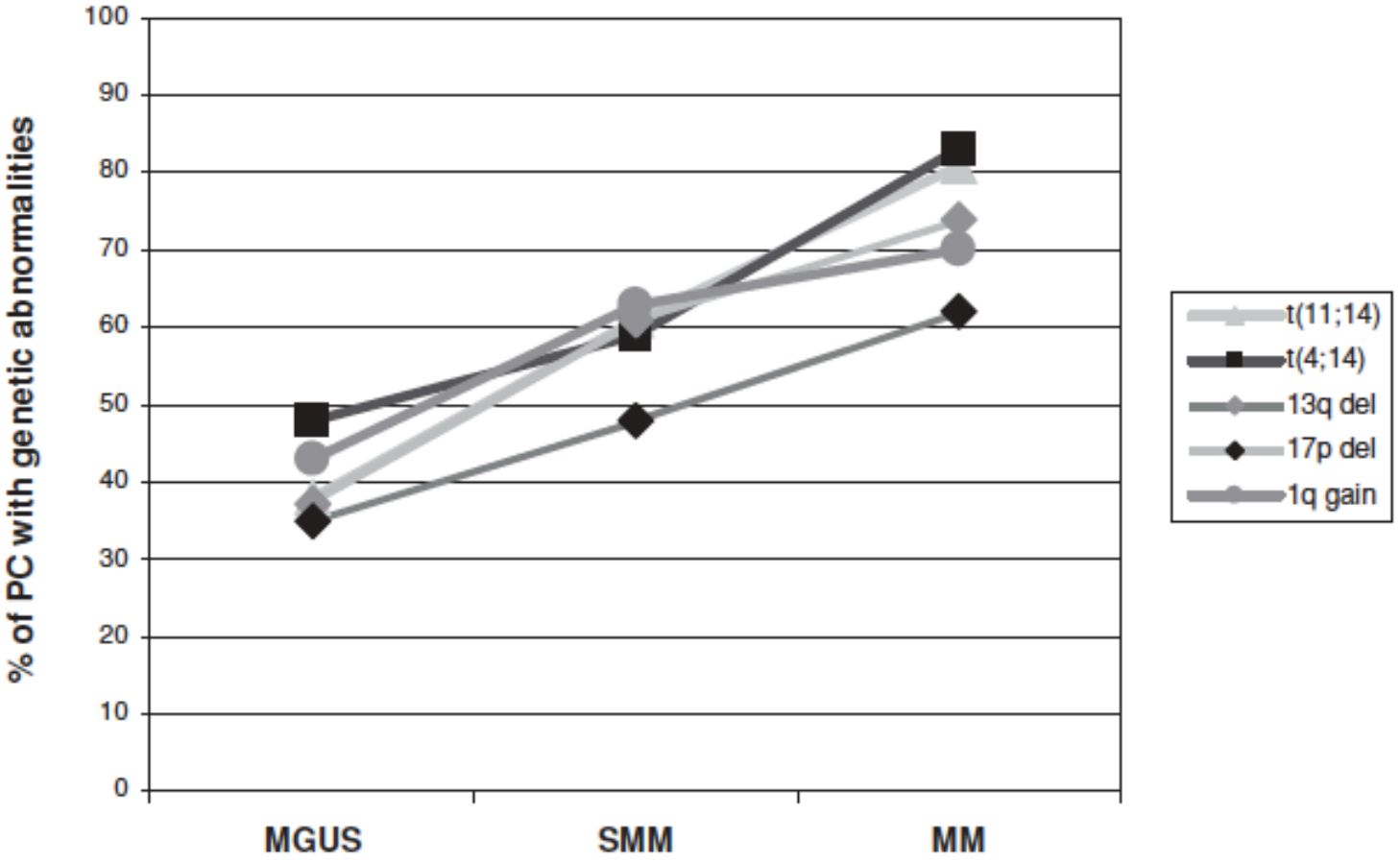
Clonal expansion



Lopez-Corral, L., et al. (2011) Clin Cancer Res 17(7): 1692-1700.

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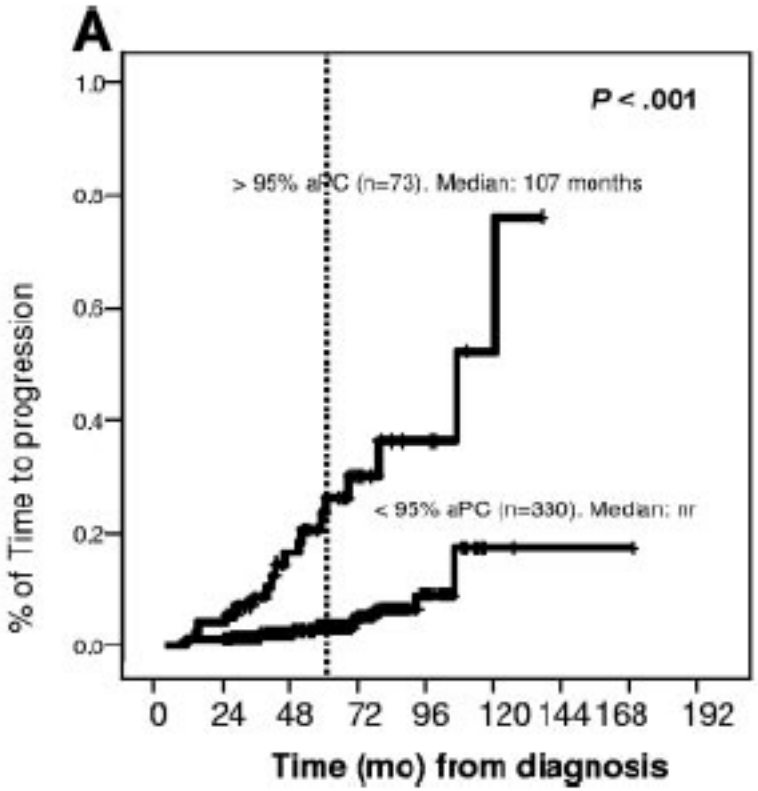
Increasing proportion of abnormal PCs

Table 2. Aberrant phenotypic profile in SMM and MGUS patients

CD45	CD19	CD56	%
–	–	++	50
–	–	–	24
–/dim	–	+	11
–	+	++	8
Dim	–	–	5
–	+	–	1
+	Dim	++	1



Perez-Persona, E., et al. BLOOD, VOLUME 110, NUMBER 7

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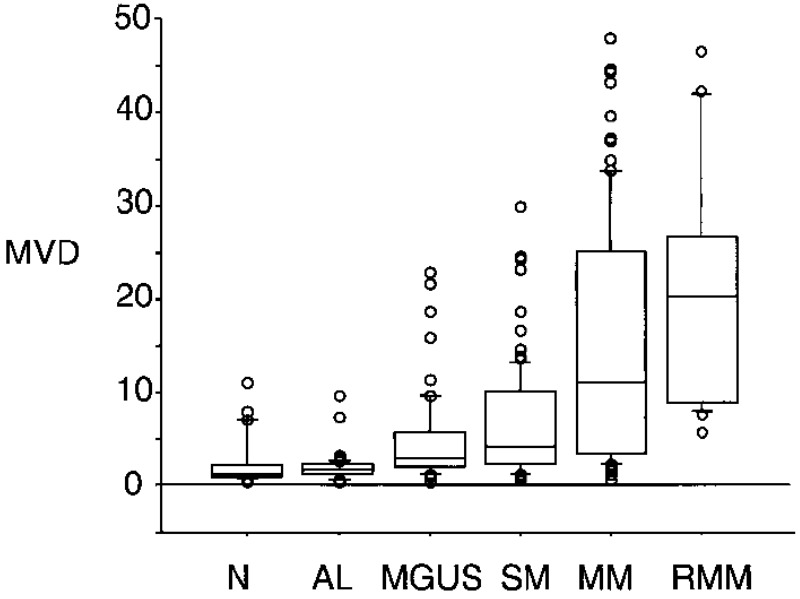
Other phenotypic markers

- Expression of a wide panel of antigens have been used to identify the “malignant plasma cell”:
  - CD38/ CD45/ CD56/ CD19/ CD117/ CD27/ CD28
- Proportion of CD45- PCs increase with disease progression
- CD200 + PCs are significantly higher in MM compared with MGUS

Paiva, B., et al. (2010) Cytometry B Clin Cytom **78**(4): 239-252, Kumar, S., et al. (2005). " Leukemia **19**(8): 1466-1470.Olteanu, H., et al. (2012). Am J Clin Pathol **138**(6): 867-876.

Angiogenesis and progression



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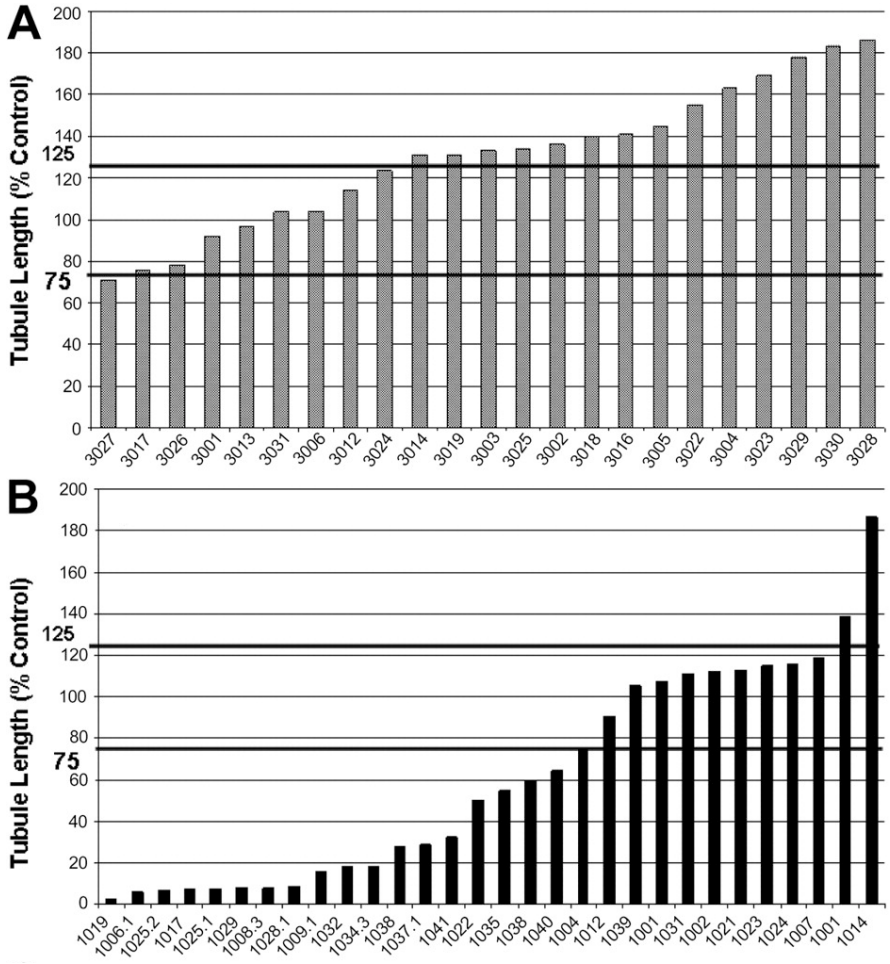

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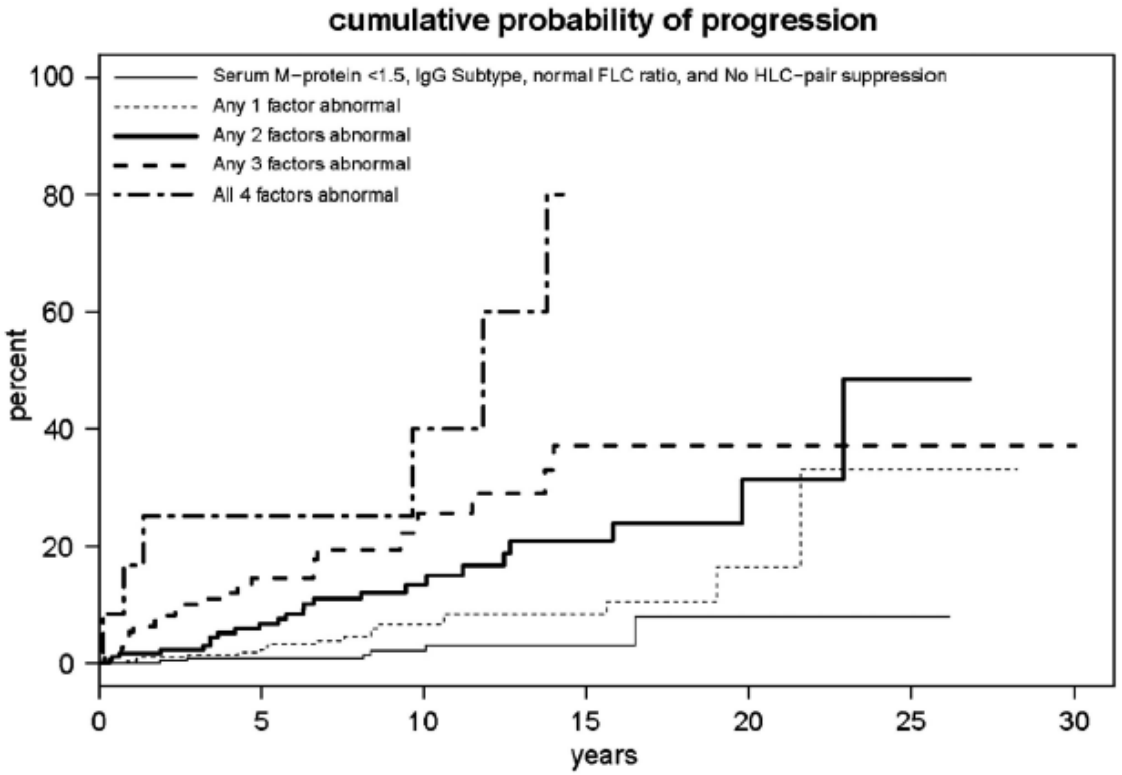
Rajkumar et al, Clinical Cancer Research 6, 3111, (2000); Kumar, S. et al. Blood 2004;104:1159-1165

Suppression of uninvolved immunoglobulin pair

Model	*Prognostic factor*	*Hazard ratio (95% CI)*	*P-value*
	HLC-pair suppression	1.8 (1.1, 3.0)	0.018
	Serum M-spike $\geqslant$1.5 gm/dl	2.3 (1.5, 3.8)	<0.001
	Abnormal FLC κ/λ ratio	2.0 (1.2, 3.4)	0.007
	IgA or IgM heavy chain	2.7 (1.6, 4.6)	<0.001



Katzmann, J. A., et al Leukemia 27(1): 208-212.

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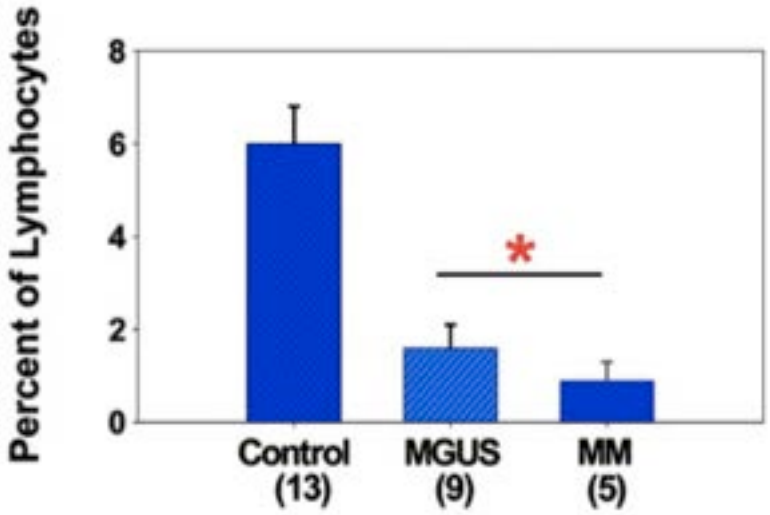
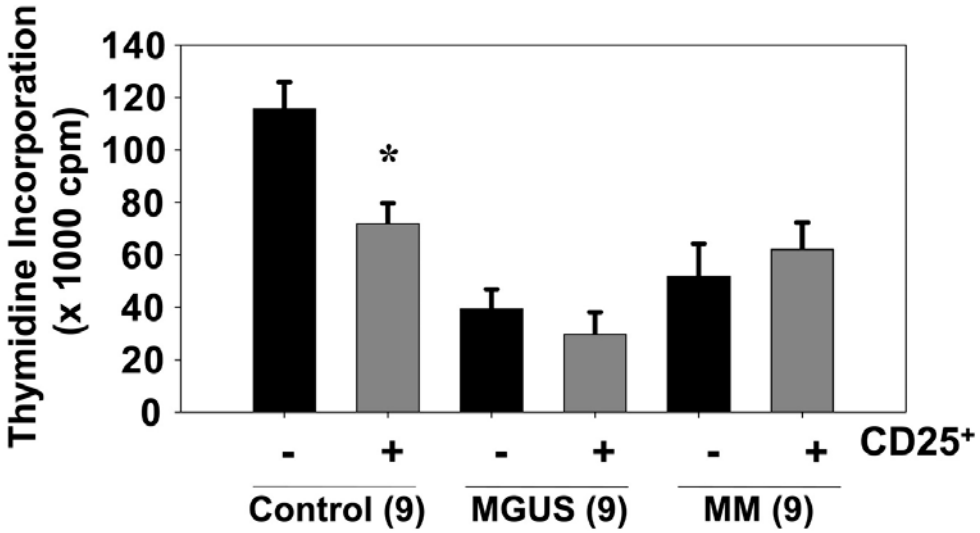
Alterations in T-cell function

Significantly decreased number of *FOXP3*$^{+}$ T_{reg} cells in MGUS



Lack of suppression of T-cell proliferation by Treg cells in MGUS



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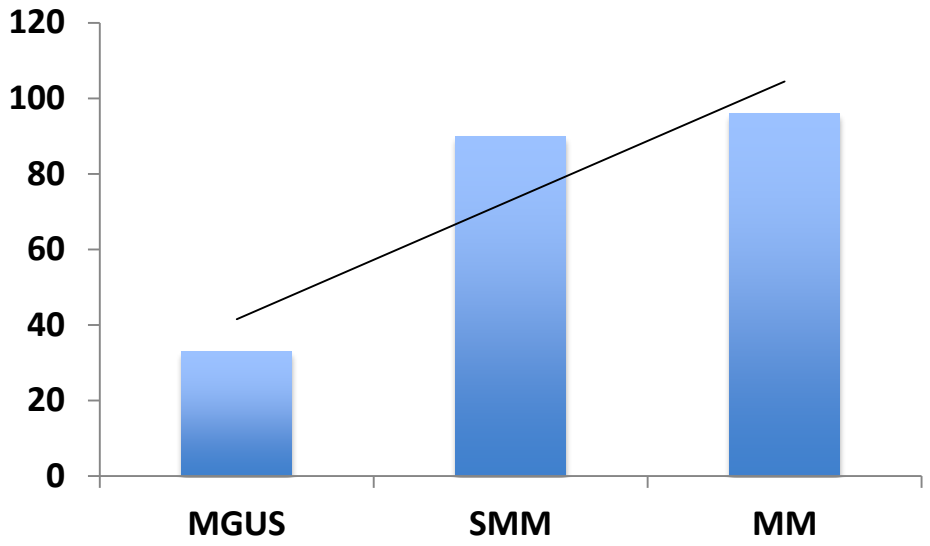
Prabhala R H et al. Blood 2006;107:301-304

FLC abnormality %

- Abnormal FLC ratio 0.26-1.65



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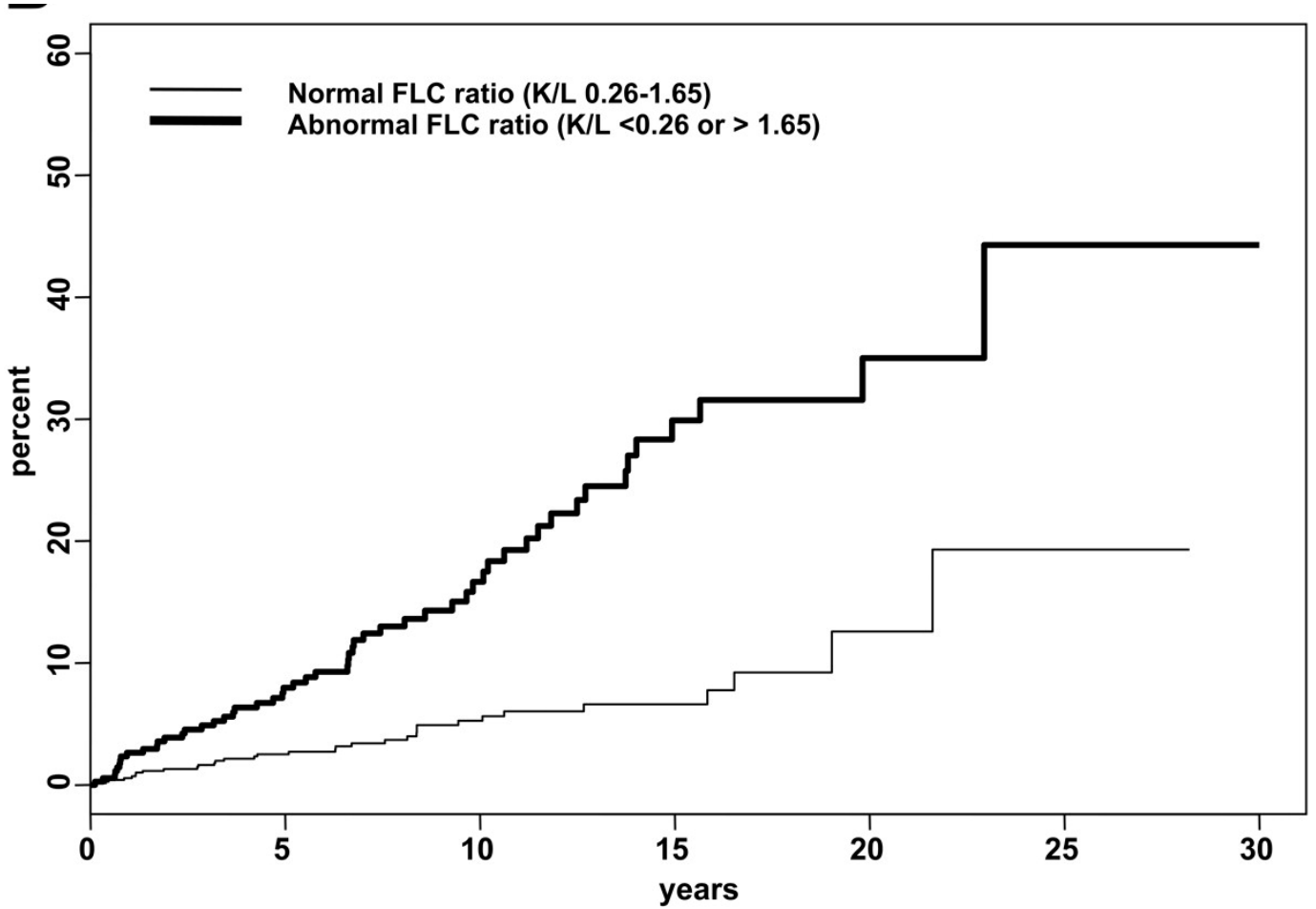
FLC ratio and the risk of progression



Rajkumar S V et al. Blood 2005;106:812-817

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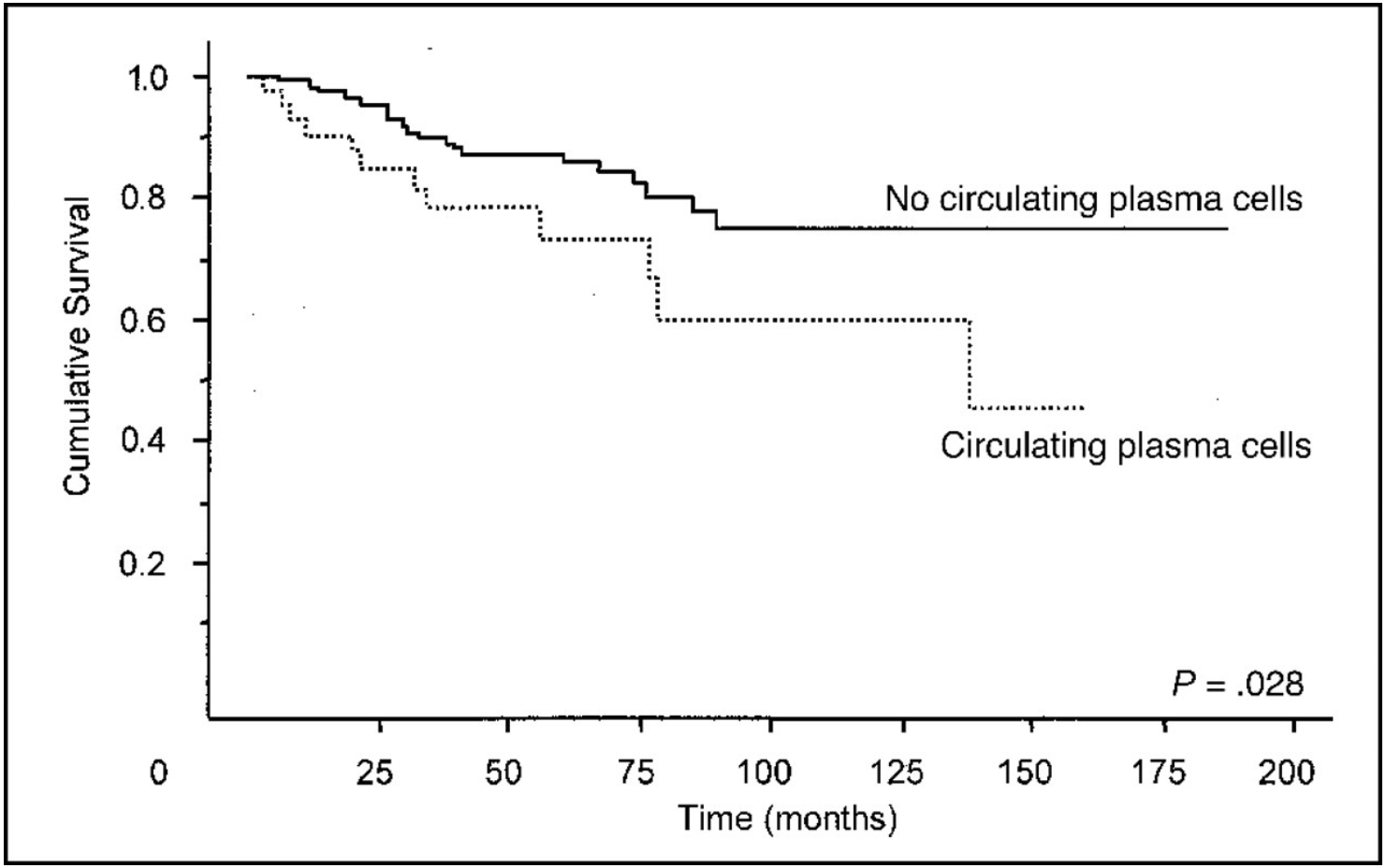
Circulating PCs and risk of progression



Kumar S et al. JCO 2005;23:5668-5674

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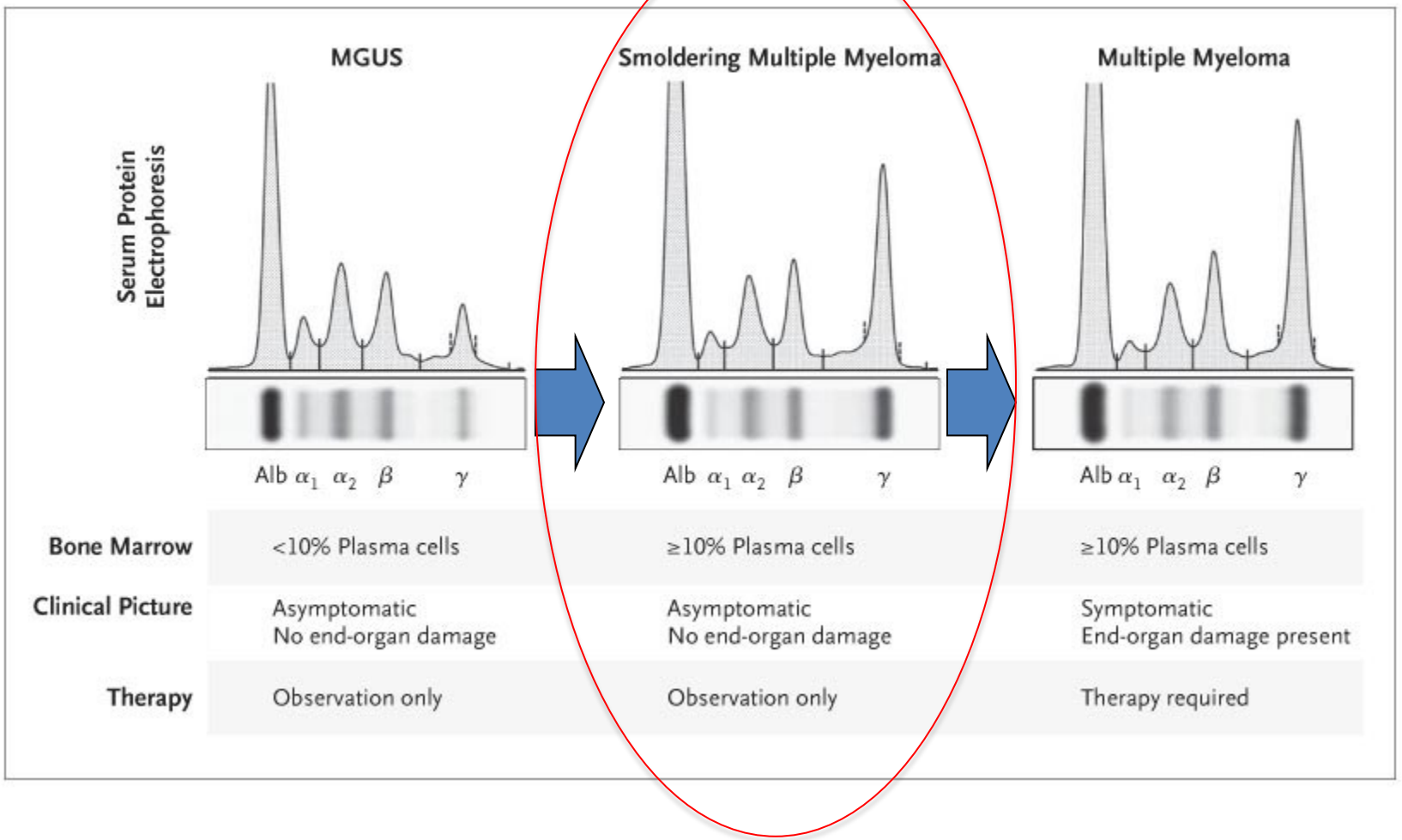
Smoldering myeloma paradigm



	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma
Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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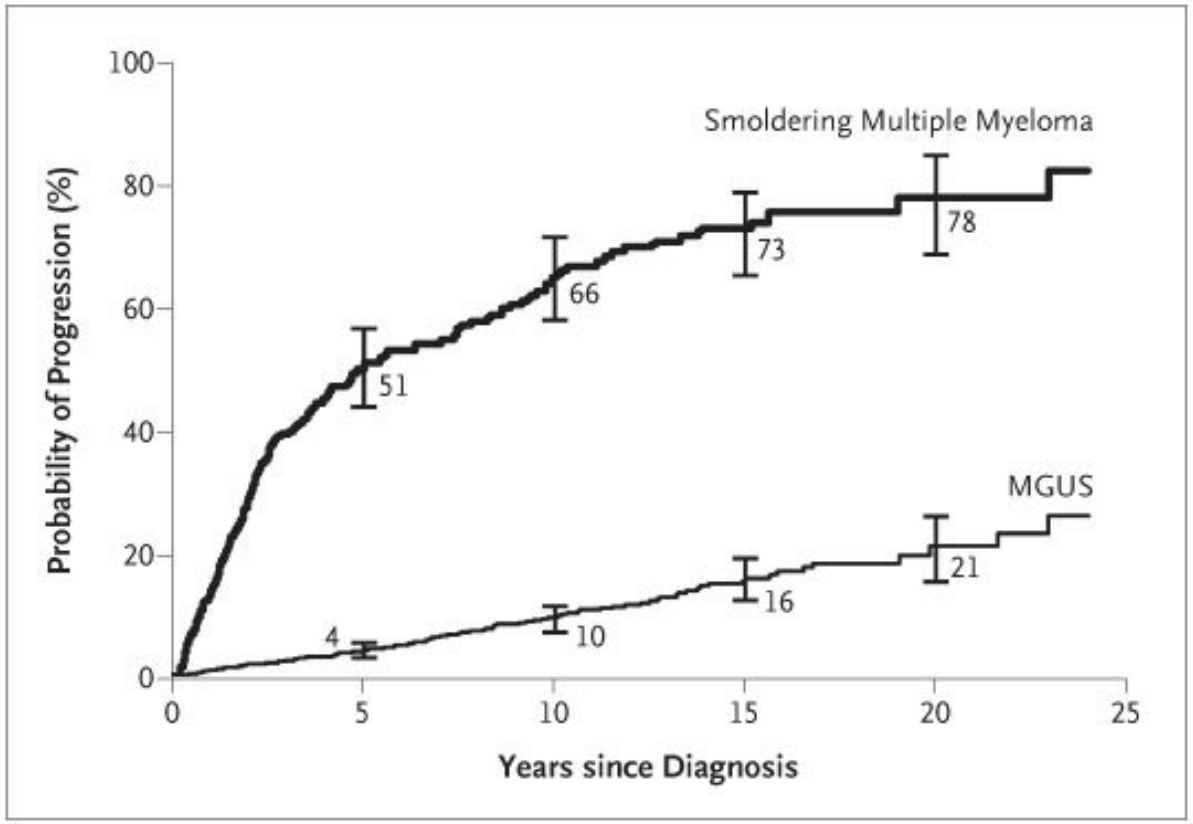
Progression to Symptomatic MM

- Risk factors: Higher M spike, higher plasma cell burden, type of M protein, Abnormal free light chain ratio, circulating plasma cells



Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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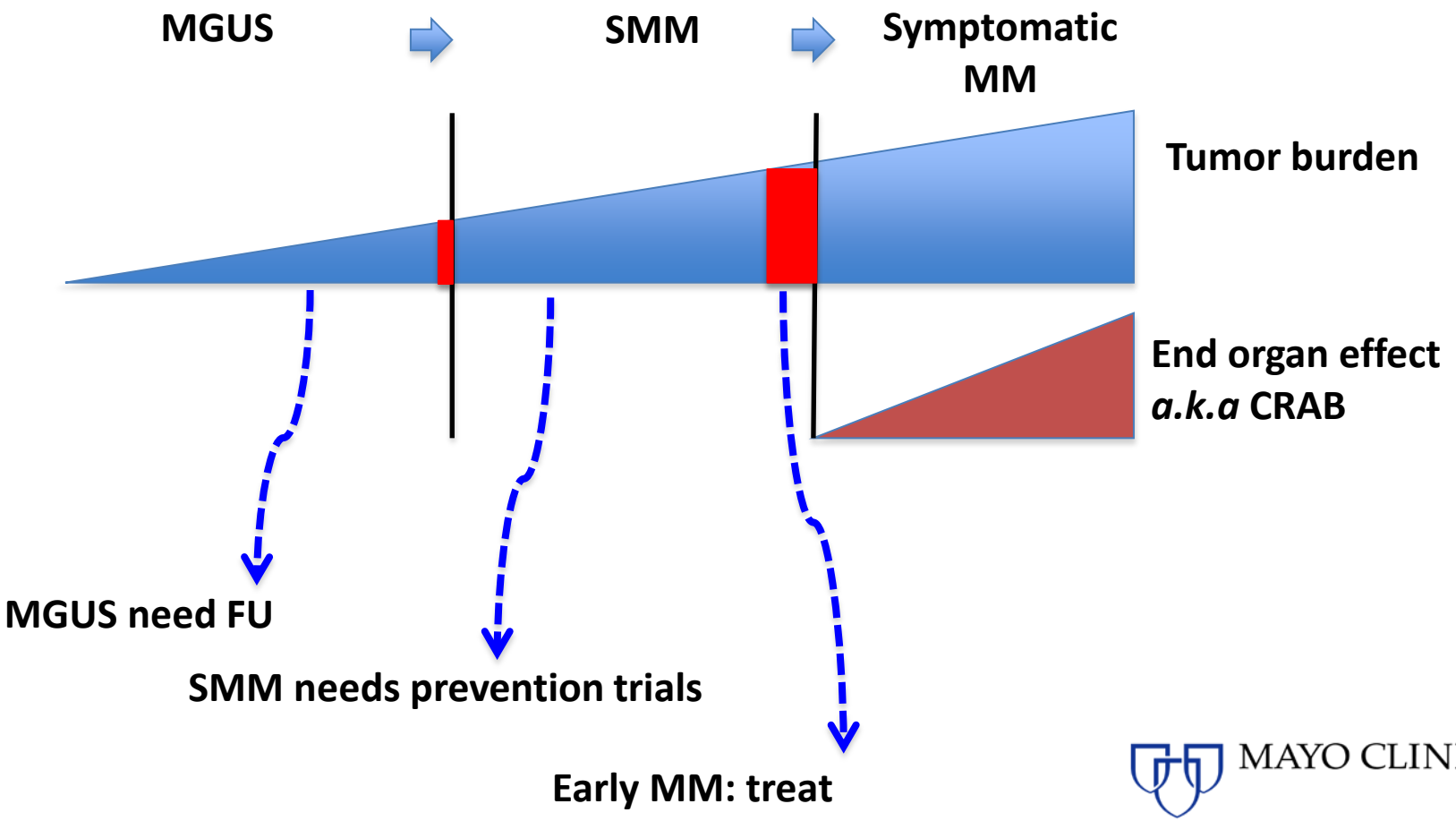
The progression paradigm…



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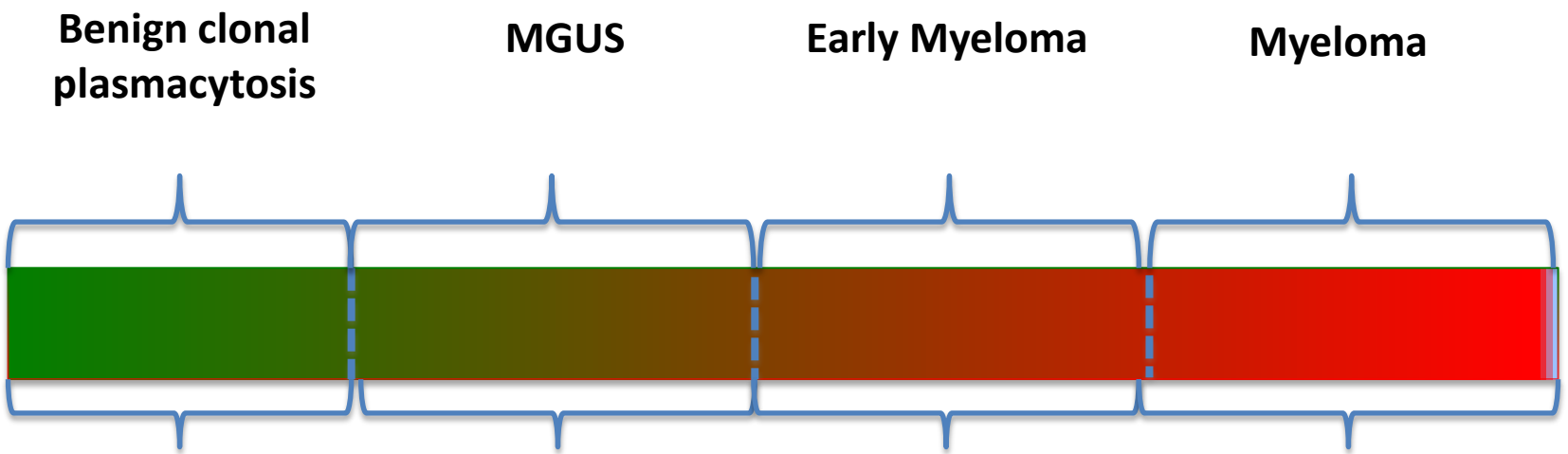
The “molecular” future…



Hyperplastic polyp → Tubular adenoma → Villous adenoma → Adenocarcinoma

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Vincent Rajkumar, MD
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Martha Lacy, MD
Nelson Leung, MD
John Lust, MD
Arleigh McCurdy, MD
Greg Nowakowski, MD
Steve Russell, MD, PhD
Steve Zeldenrust, MD, PhD

Arizona

Leif Bergsagel, MD
Rafael Fonseca, MD
Joseph Mikhael
Craig Reeder, MD
Keith Stewart, MD

Jacksonville

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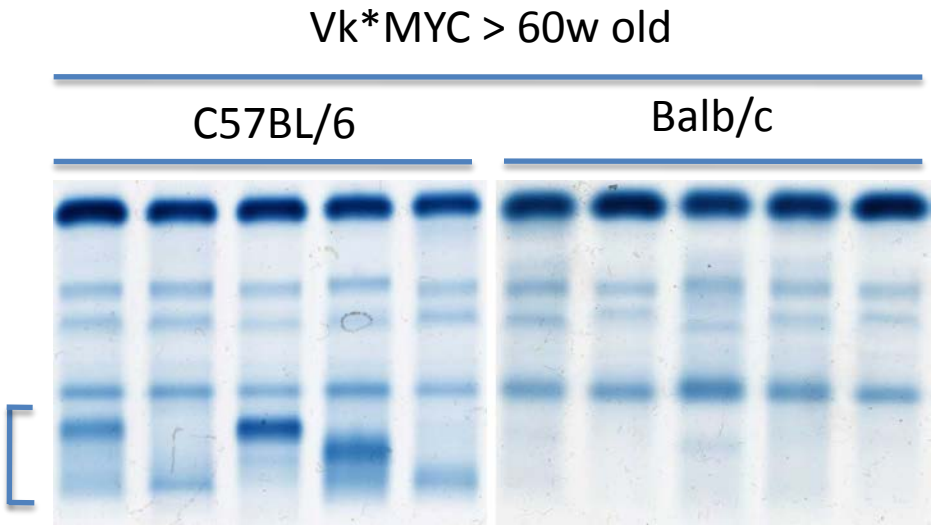
Vivek Roy, MD
Tamur Sher, MD

Thank you

MYC driven MM occurs in a mouse strain that spontaneously develops MGUS (C57Bl/6), but not in one that does not (Balb/c)



Vk*MYC generated in pure C57BL/6j strain were backcrossed > 10 times into Balb/c strain
The plasma cell content (in %) of wt and Vk*MYC mice > 60w old is shown, as well as SPEP of age matched Vk*MYC mice in both strain

Chesi et al. unpublished

MAYO CLINIC