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Rafael Fonseca MD, Mayo Clinic

The classification of myeloma; subtypes of the disease

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Disclosures

- **Consulting: AMGEN, Genzyme, BMS, Otsuka, Celgene, Lilly, Medtronic**
- **Speakers Bureaus: None**
- **Research: Cylene, Proteolix**
- **Patent for FISH based prognostication in MM**

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Classification schemes

Leukemia (2009) 23, 2210–2221

www.nature.com/leu

SPOTLIGHT REVIEW

International Myeloma Working Group molecular classification of multiple myeloma: spotlight review

R Fonseca[1], PL Bergsagel[1], J Drach[2], J. Shaughnessy[3], N Gutierrez[4], AK Stewart[1], G Morgan[5], B Van Ness[6], M Chesi[1], S Minvielle[7], A Neri[8], B Barlogie[3], WM Kuehl[9], P Liebisch[10], F Davies[5], S Chen-Kiang[11], BGM Durie[12], R Carrasco[13], Orhan Sezer[14], Tony Reiman[15], Linda Pilarski[16] and H Avet-Loiseau[7]

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Classification schemes

- **Biology classification**
  - Pathophysiology — **Translocations**
  - Progression events — **MGUS to MM**
- **Prognostic classification**
  - Baseline features — **t(4;14)**
  - Natural history — **-17p13**
- **Predictive classifications** — **TRAF3**
  - Therapy specific

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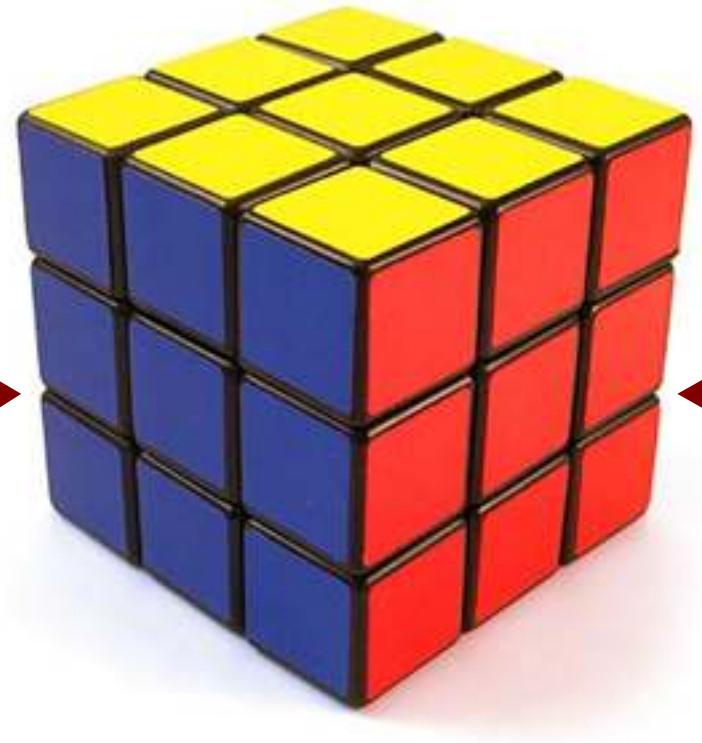
Biologic classification



Predictive classification

Prognostic classification

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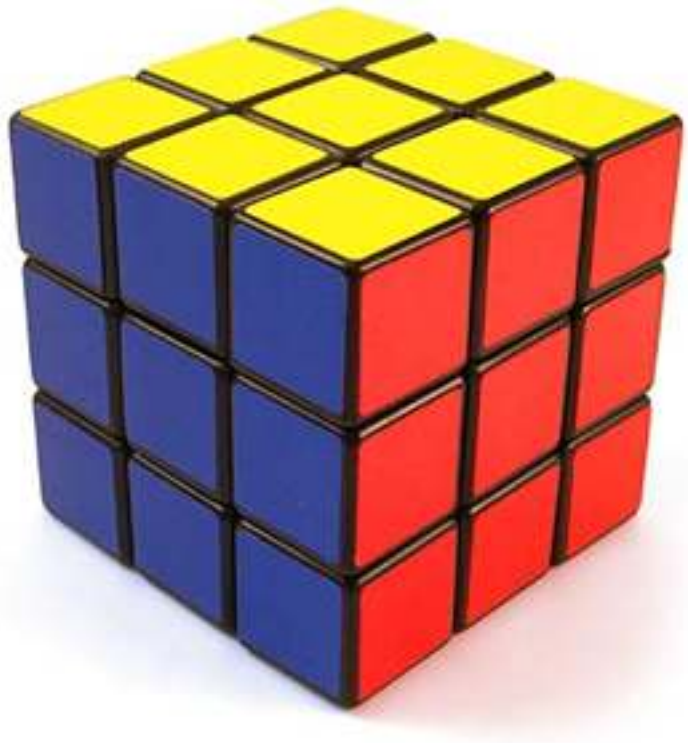
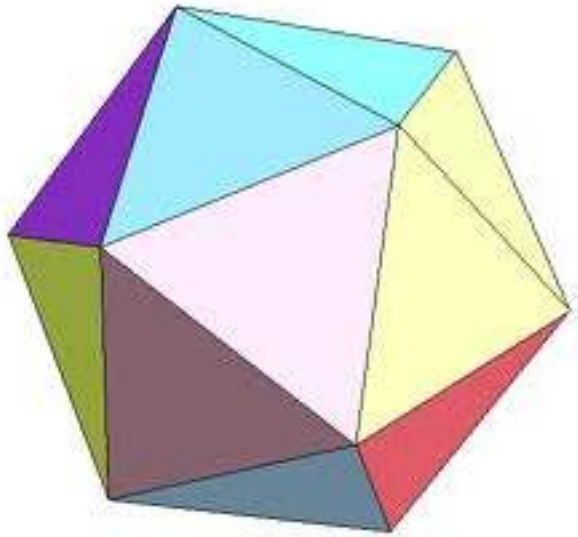
Classification schemes





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Classification schemes; How many?

- Global ploidy (H-MM vs NH-MM)
- Translocation
- Progression (-17, 1q+/1pdel)
- NF-kB activated or not
- Mutation; common (ras,p53) & rare (B-RAF)
- Epigenetic subtypes
- Subclones
- miRNA classifiers (previously discussed)
- Truly multidimensional

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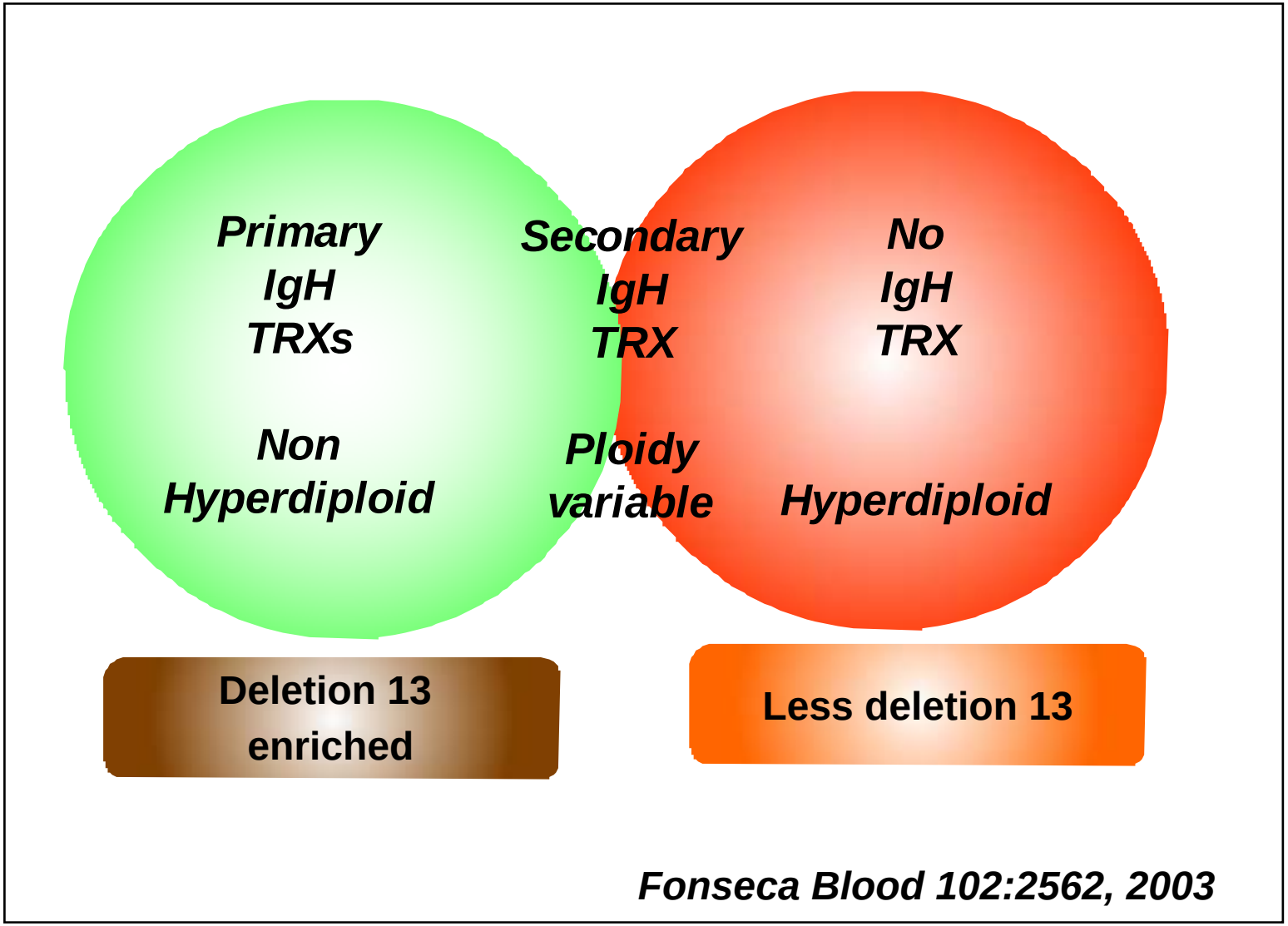
Genetic Classification of MM



Fonseca Blood 102:2562, 2003

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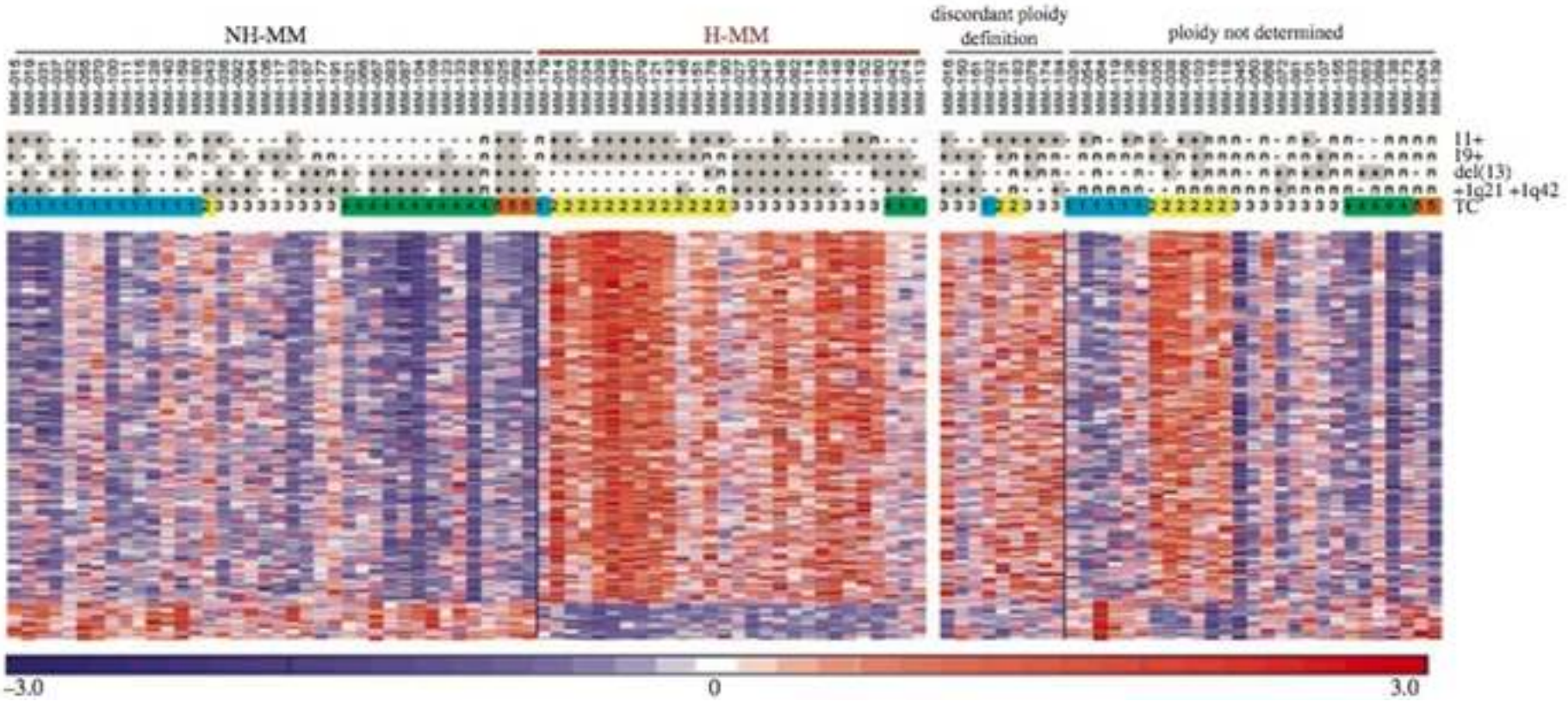
Genetic Classification of MM



Agnelli et al Brit J of Haematol, 136, 565–573
Agnelli et al Hematologica 2007 vol. 92 (1) pp. 56-65

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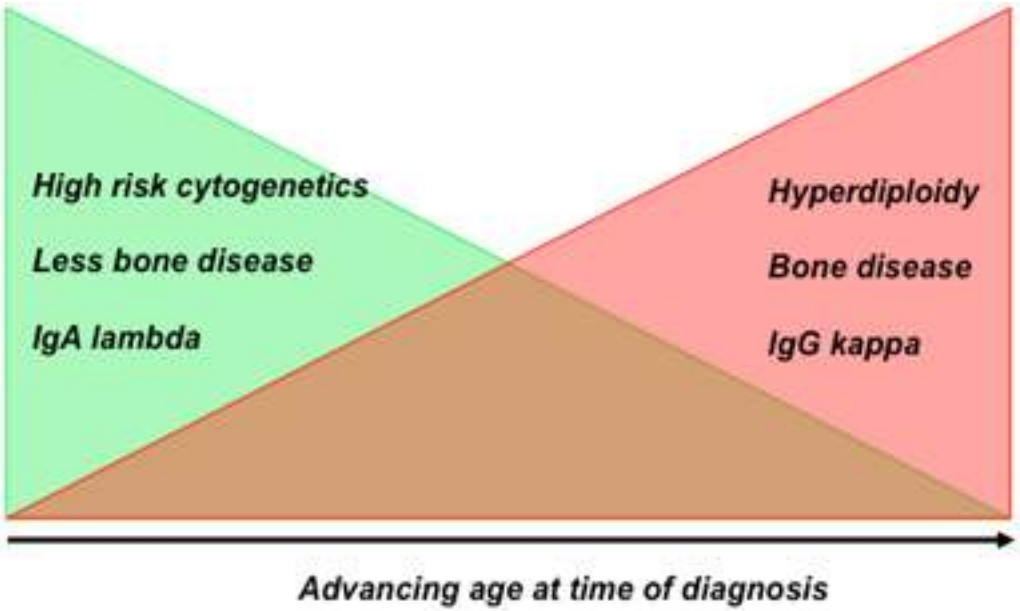
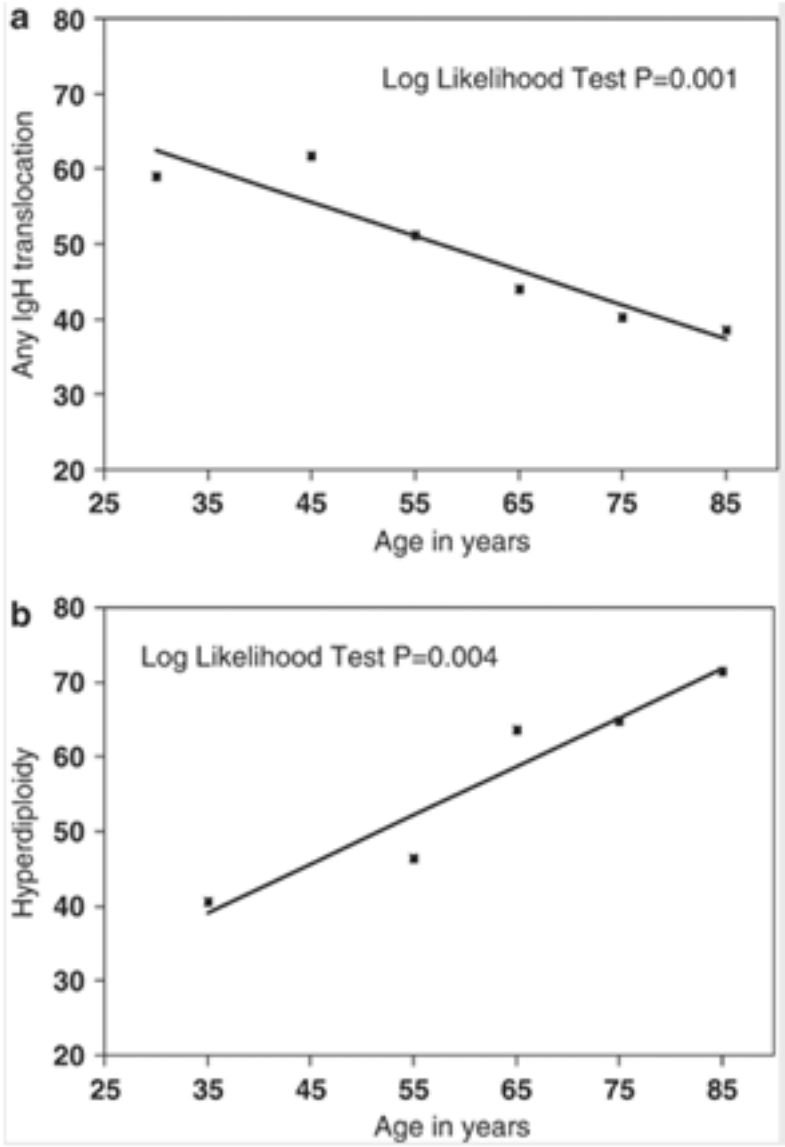
Ploidy and Age



Ross et al Leukemia (2005) 19, 1634–1642



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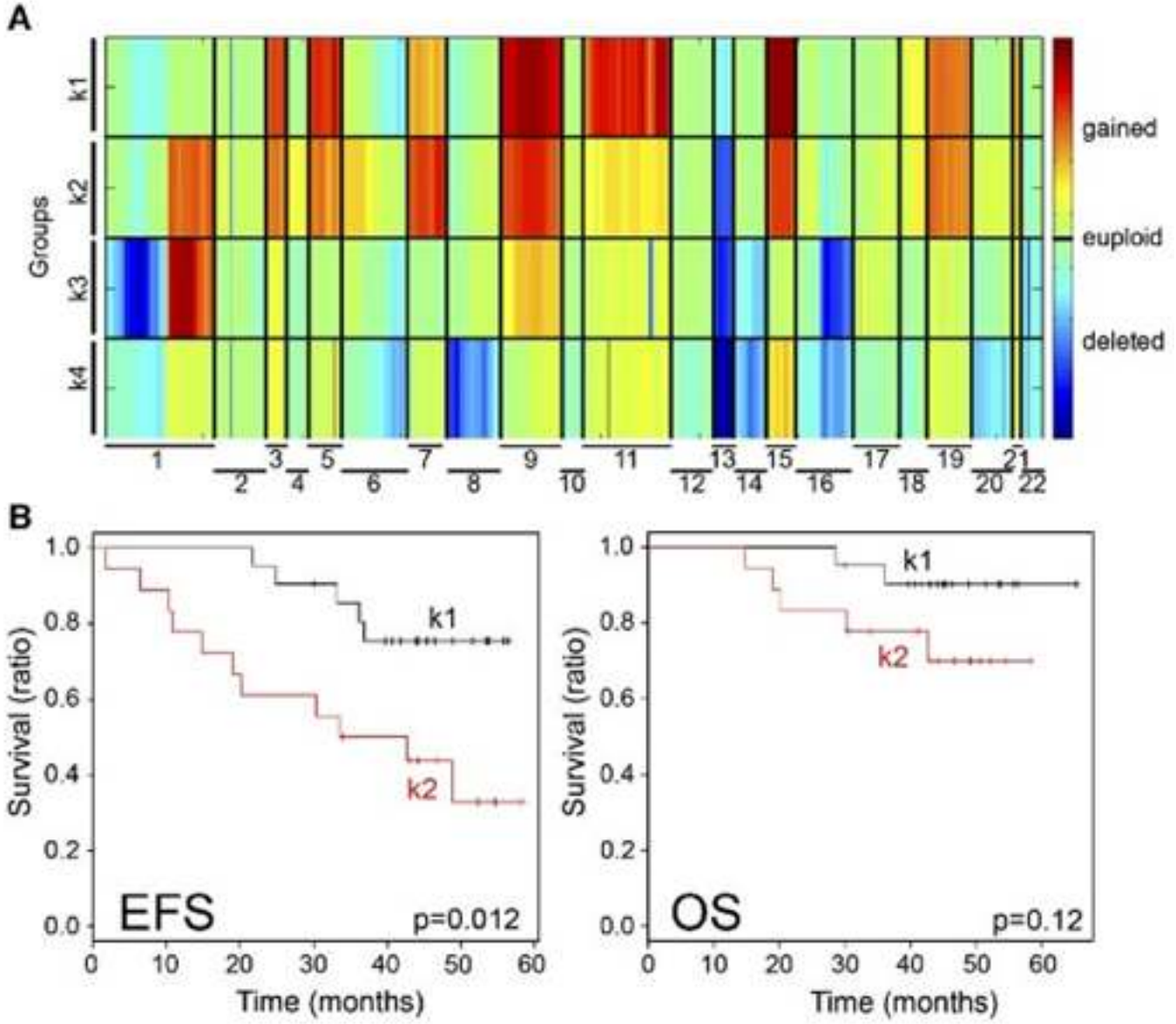
Ploidy and aCGH



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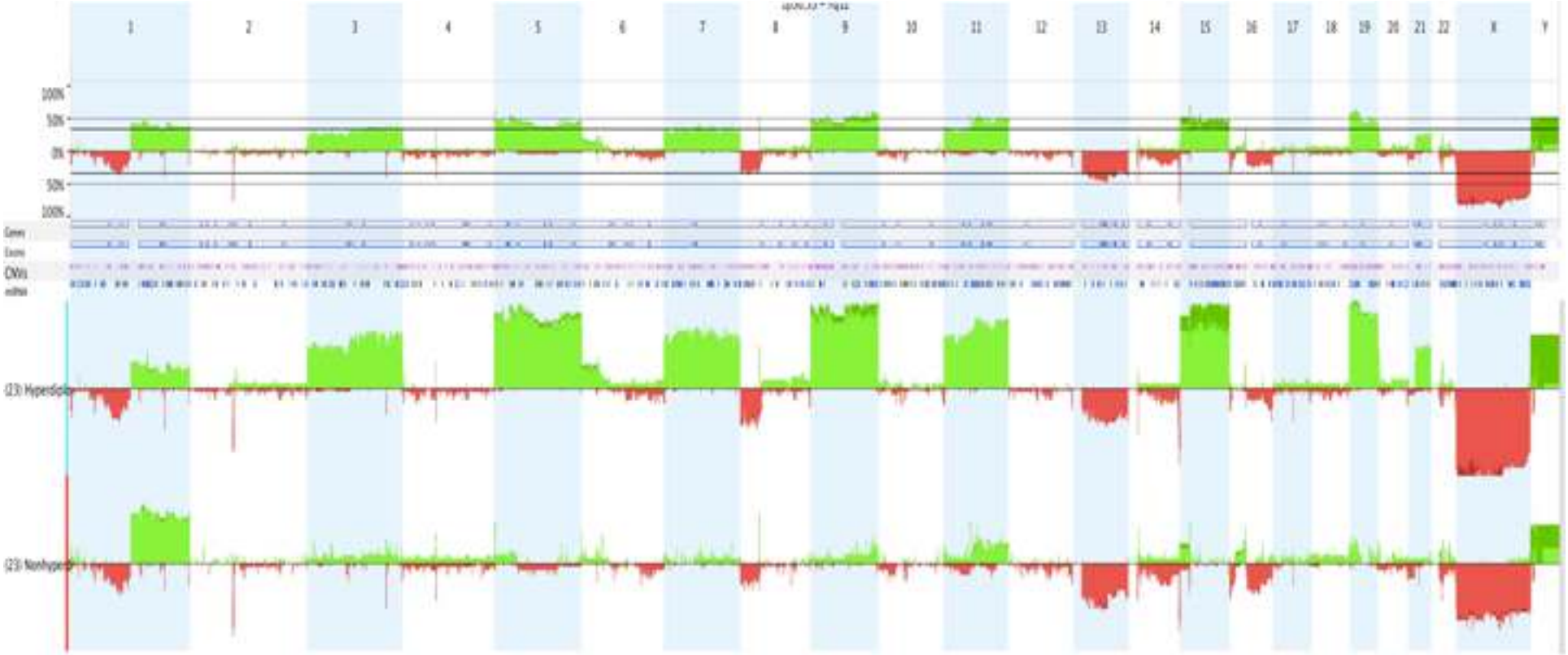
Ploidy and aCGH



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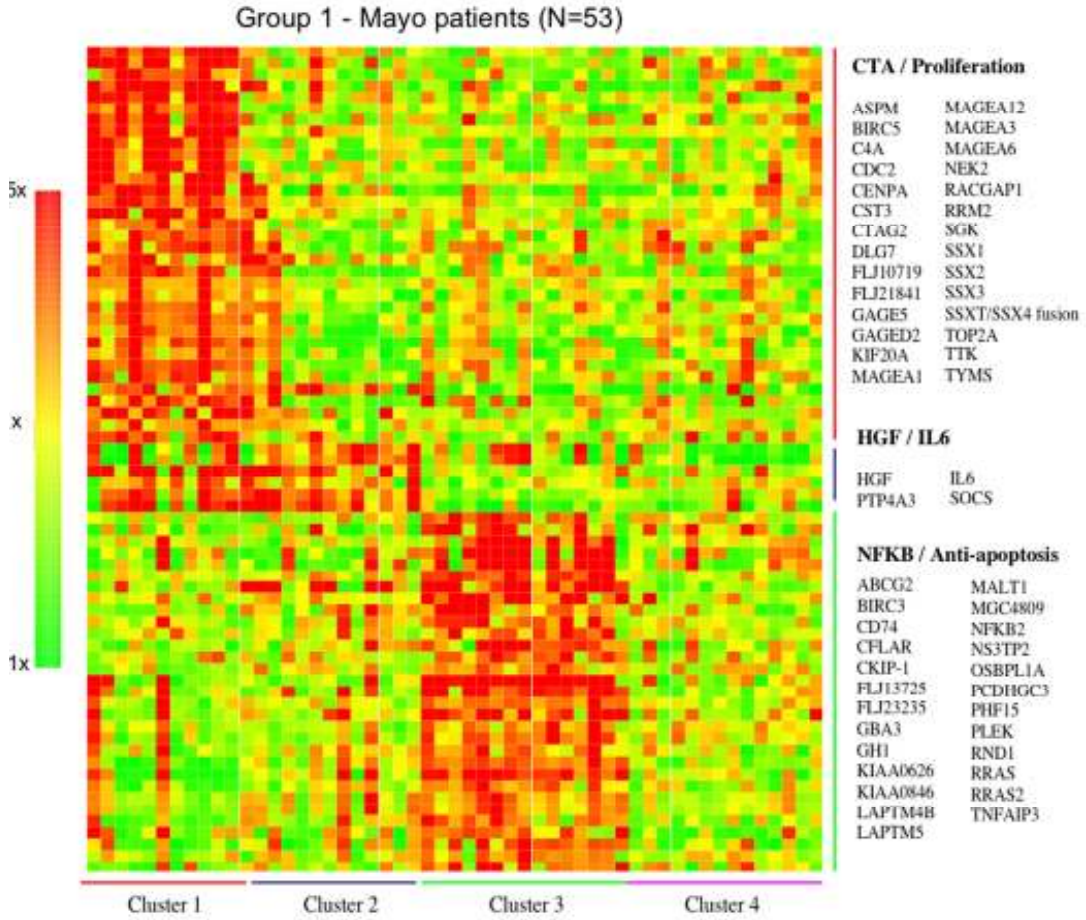
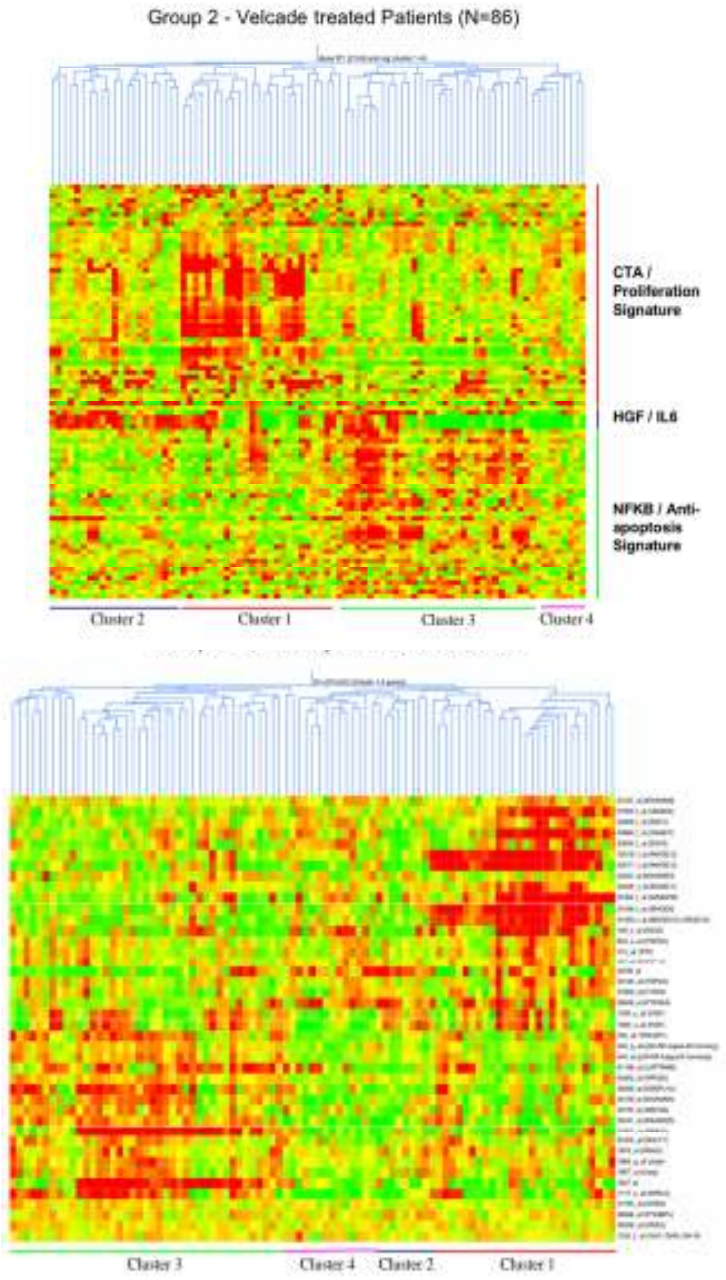
Hyperdiploid





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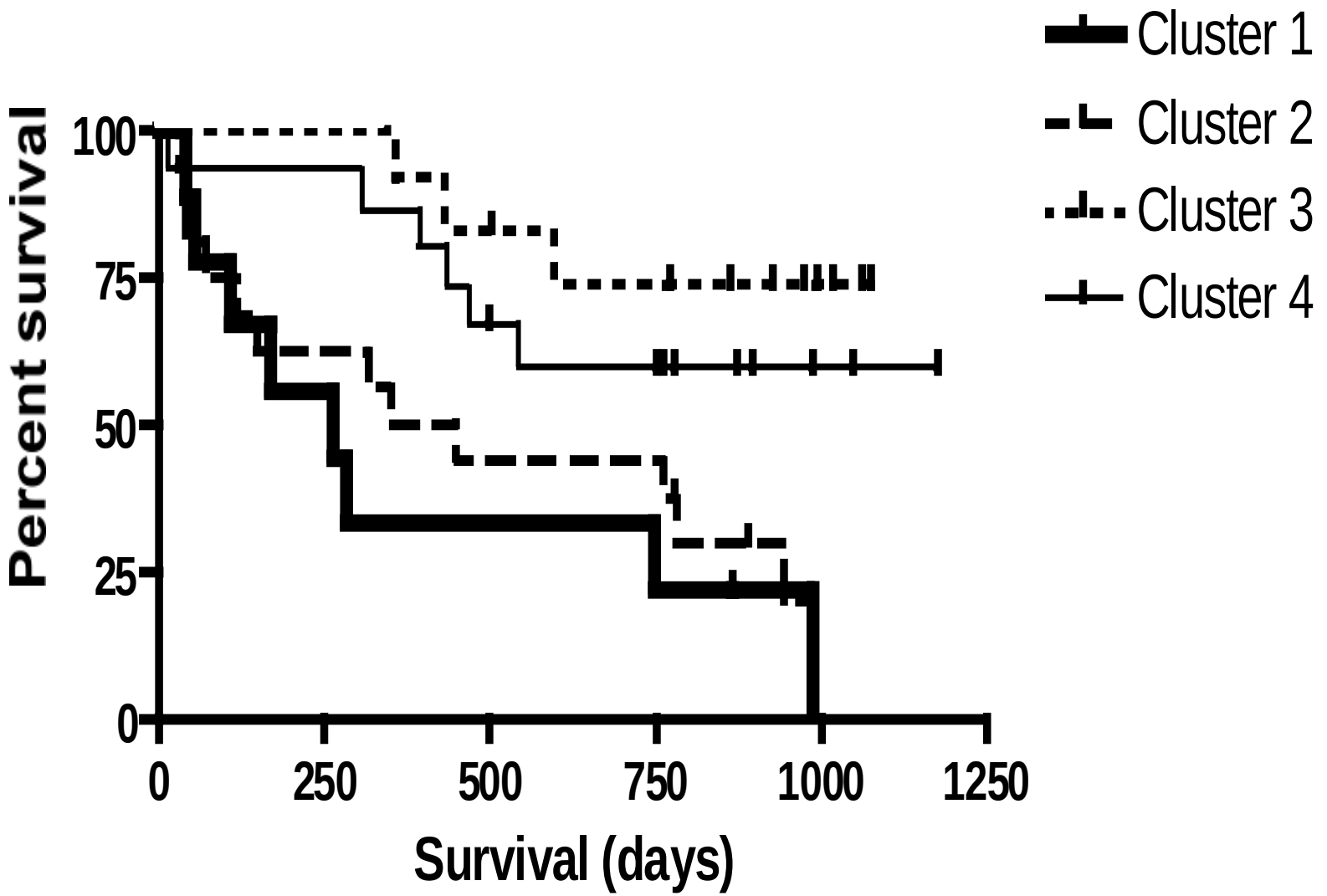
Hyperdiploidy Subgroups



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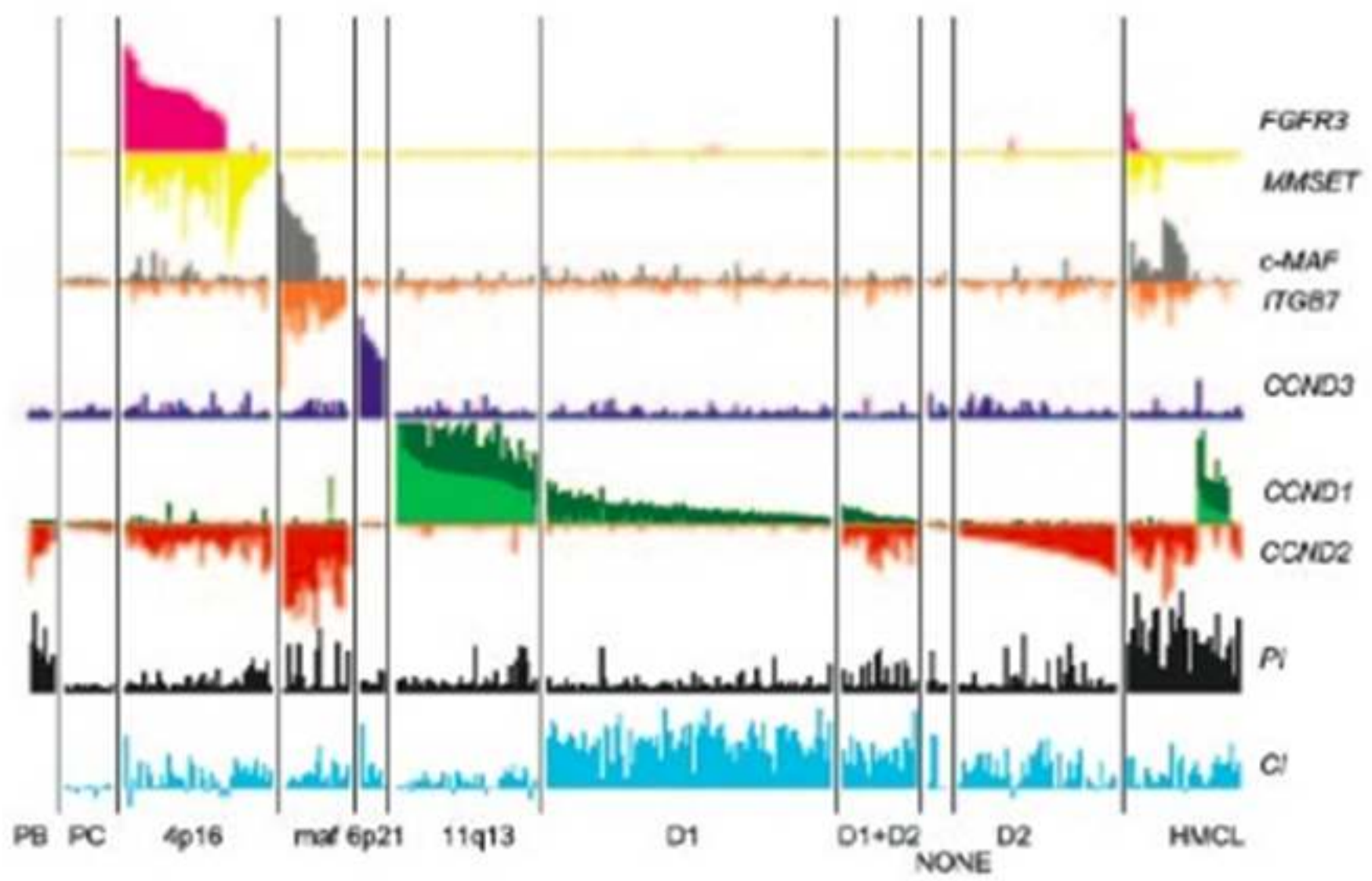
TC Classification



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Classification of MM

	Ploidy	Prognosis	H	k/l	Morph	CD20	*ras*	-13	Bone DKK1	CCND
t(11;14) *(CCND3)*	NH	Good	G	λ	LPL	+++	++	-/+	++	D1 D3
t(14;16) (other *MAF*)	NH	Poor	A	λ	PB	-	-	++	+/-	D2
t(4;14)	NH/h	Poor	A	λ	PB	-	-	+++	+/-	D2

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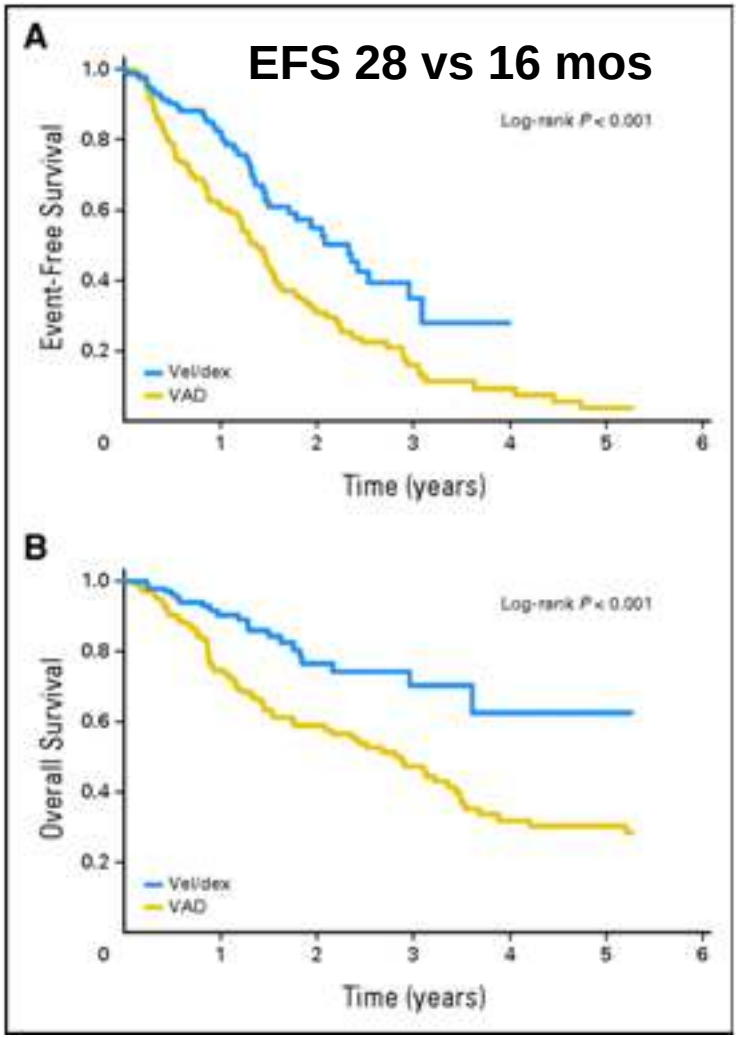
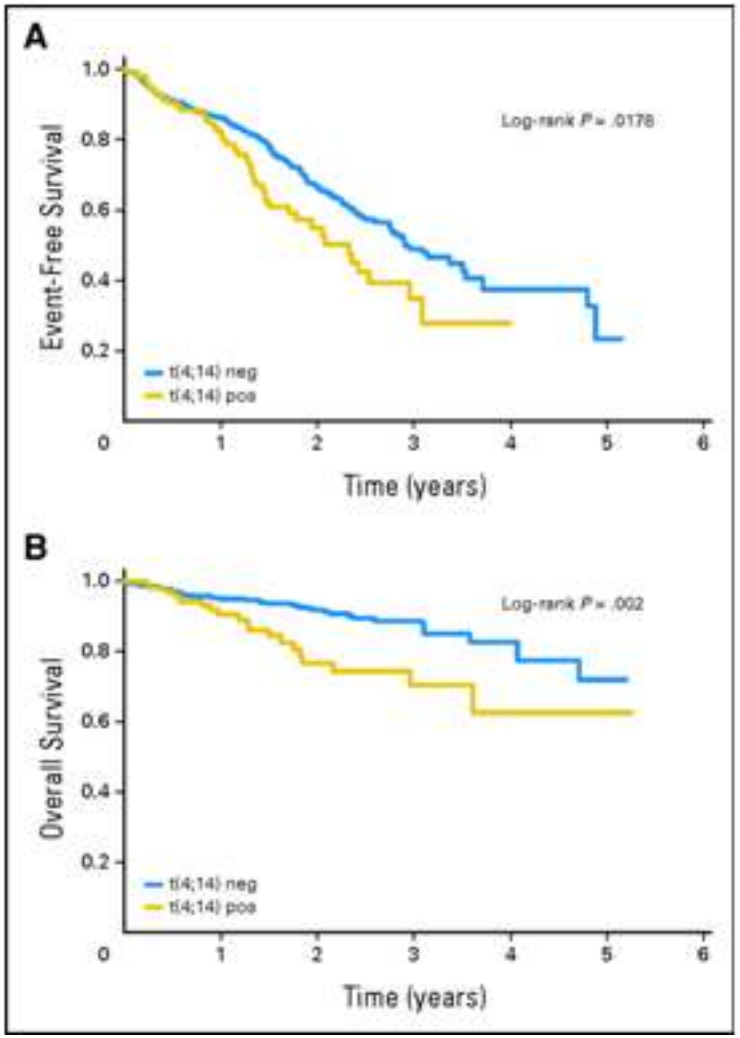
VAD vs VD in t(4;14)

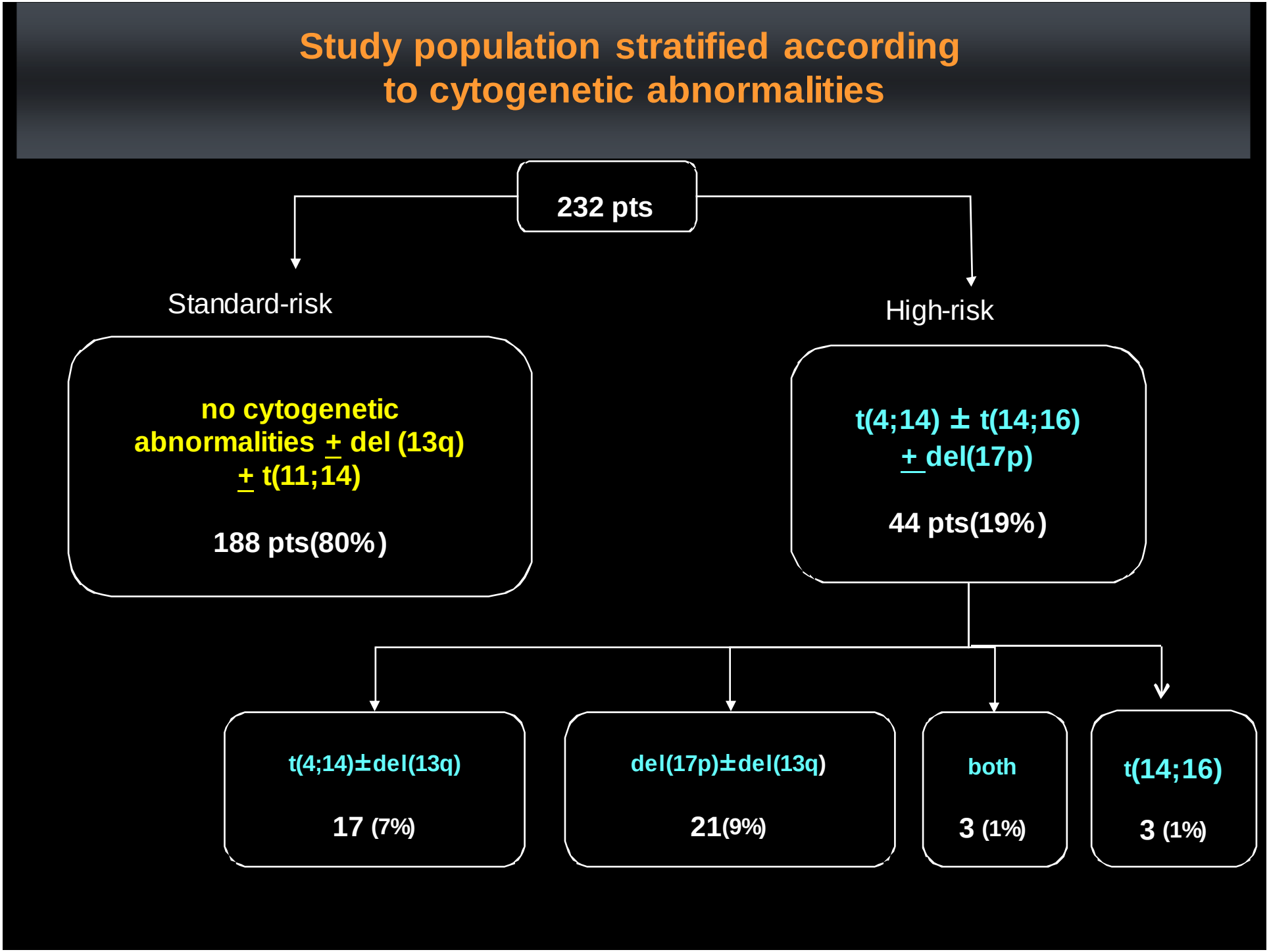


t(4;14) vs not; VD Rx

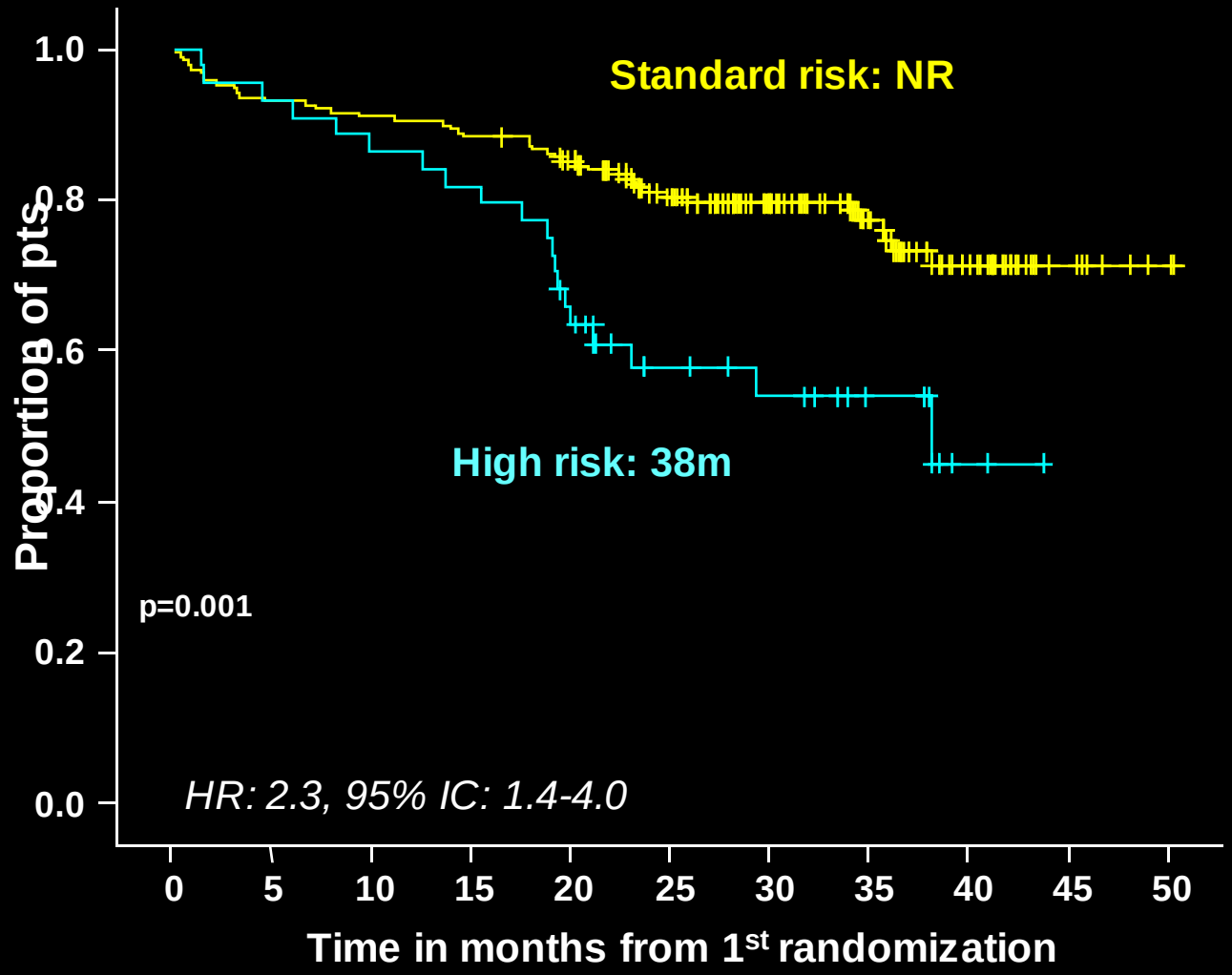


Avet-Loiseau H et al. JCO 2010;28:4630-4634

Study population stratified according to cytogenetic abnormalities



Overall survival according to cytogenetic abnormalities



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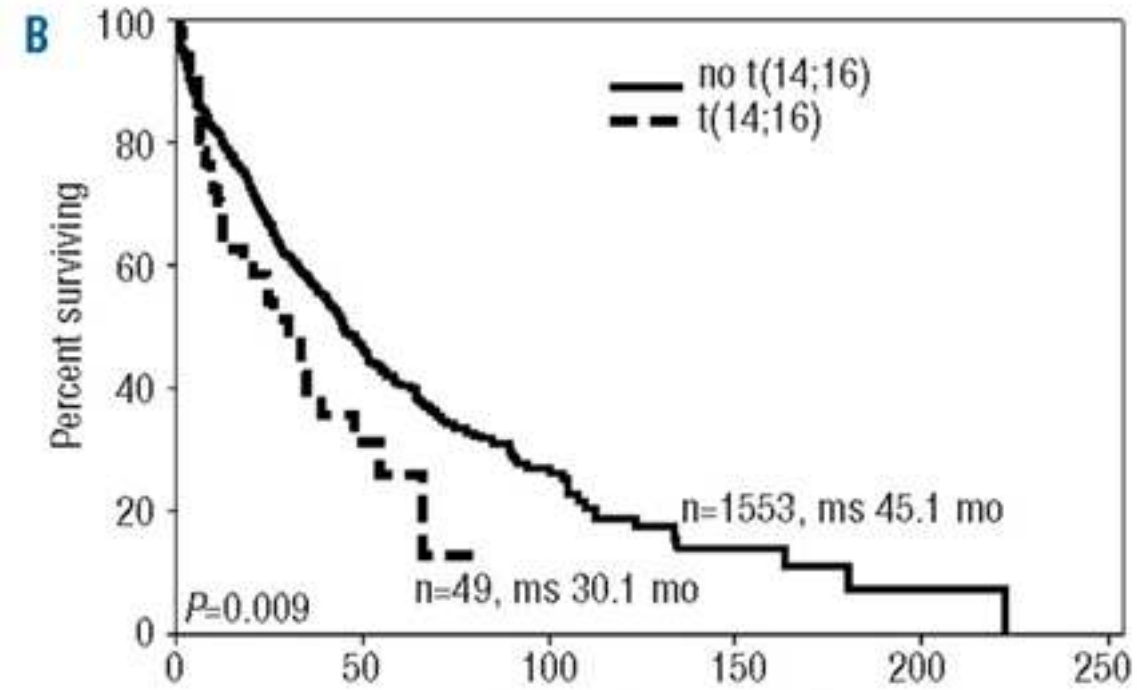
Is the t(14;16) prognostic?

Brief report

Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor?

Hervé Avet-Loiseau,[1] Florent Malard,[1] Loic Campion,[2] Florence Magrangeas,[1] Catherine Sebban,[3] Bruno Lioure,[4] Olivier Decaux,[5] Thierry Lamy,[6] Laurence Legros,[7] Jean-Gabriel Fuzibet,[8] Mauricette Michallet,[9] Bernadette Corront,[10] Pascal Lenain,[11] Cyrille Hulin,[12] Claire Mathiot,[13] Michel Attal,[14] Thierry Facon,[15] Jean-Luc Harousseau,[16] Stephane Minvielle,[1] and Philippe Moreau,[17] for the Intergroupe Francophone du Myélome



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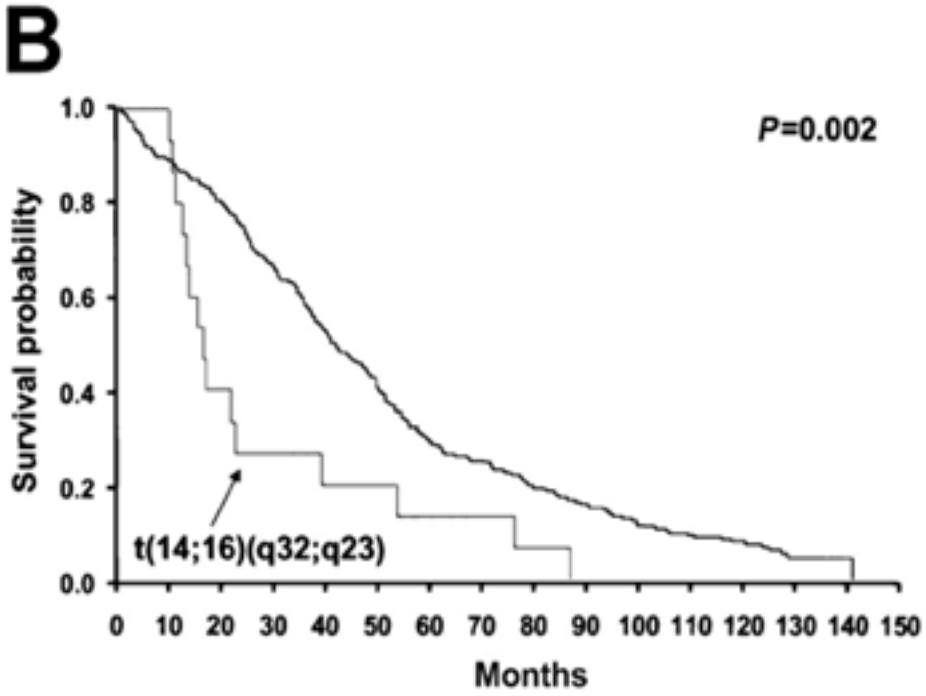
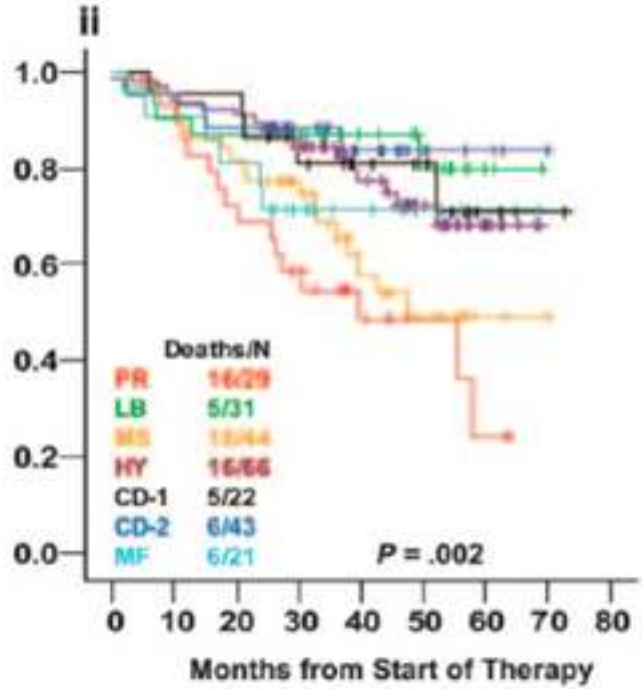
Survival by t(14;16) status





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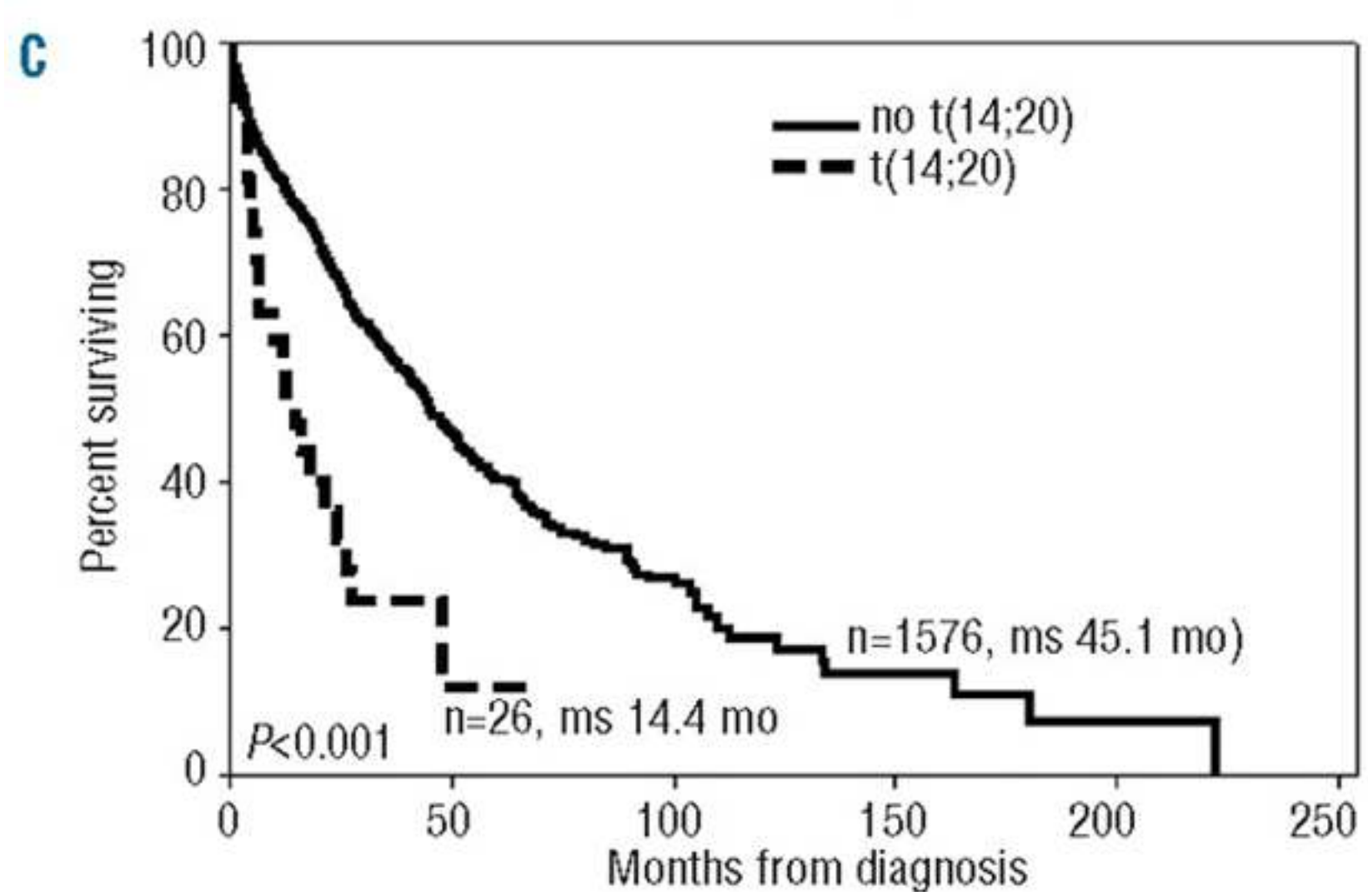
Other MAF Translocations



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Correlation Between High Risk and MAF

Table 3. Correlation of clinical parameters with risk groups in the test cohort (n = 181)

Characteristic	Low risk, %	High risk, %	*P*
Age, 65 y or older	30	23	.692
Albumin, less than 35 g/L	17	32	.163
β_2-microglobulin			
Less than 297.5 nM	57	32	.005
297.5 nM to less than 467.5 nM	23	18	
467.5 nM or more	19	50	
C-reactive protein, 4 mg/L or above	44	59	.271
LDH, 190 IU/L or above	18	59	< .001
Cytogenetic abnormalities	27	77	< .001
GEP-based translocations			
CCND1	14	0	< .001
MMSET	12	23	
MAF/MAFB	7	36	
No spike	67	41	

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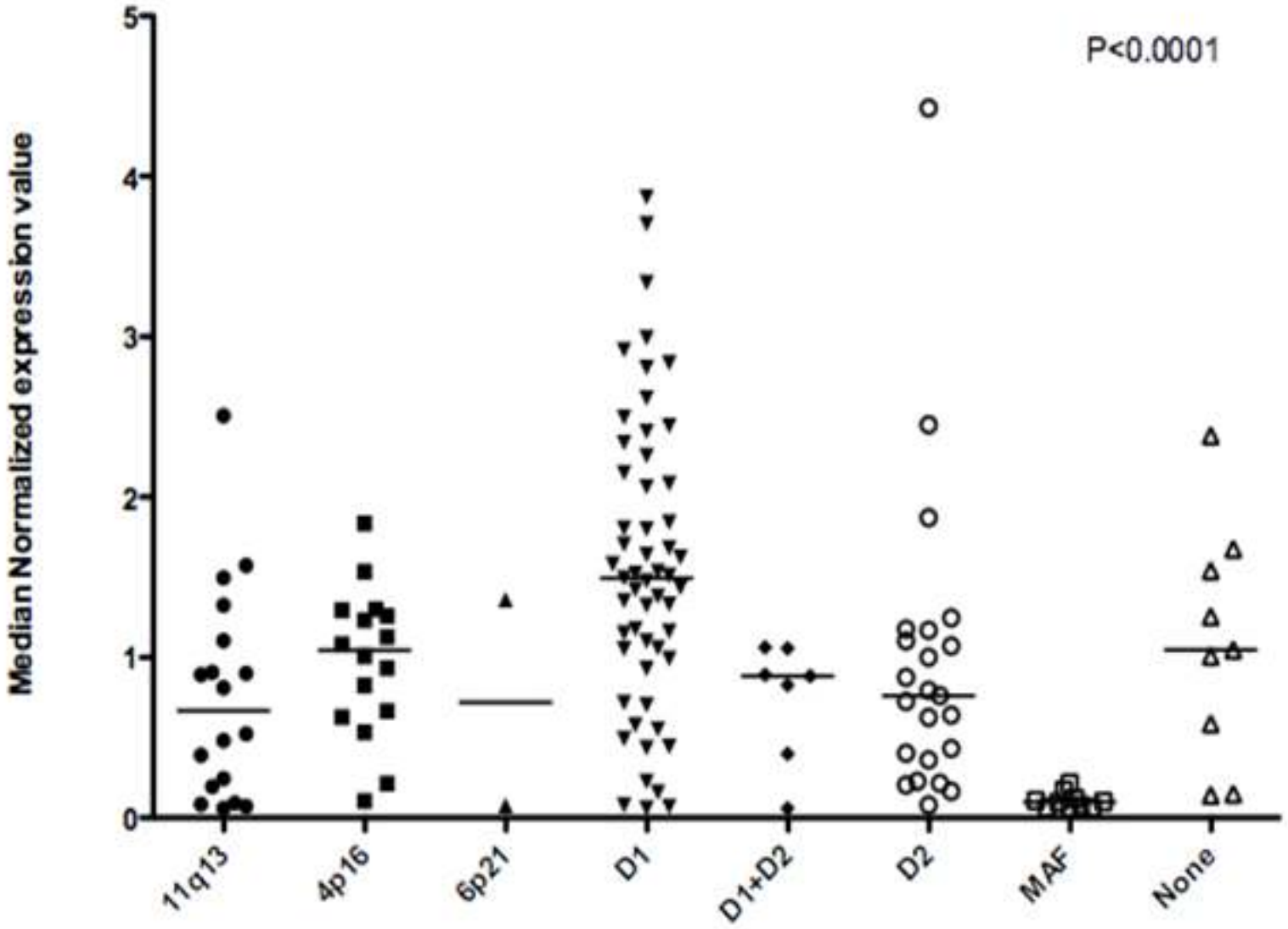
CD56 Expression by t(14;16) status



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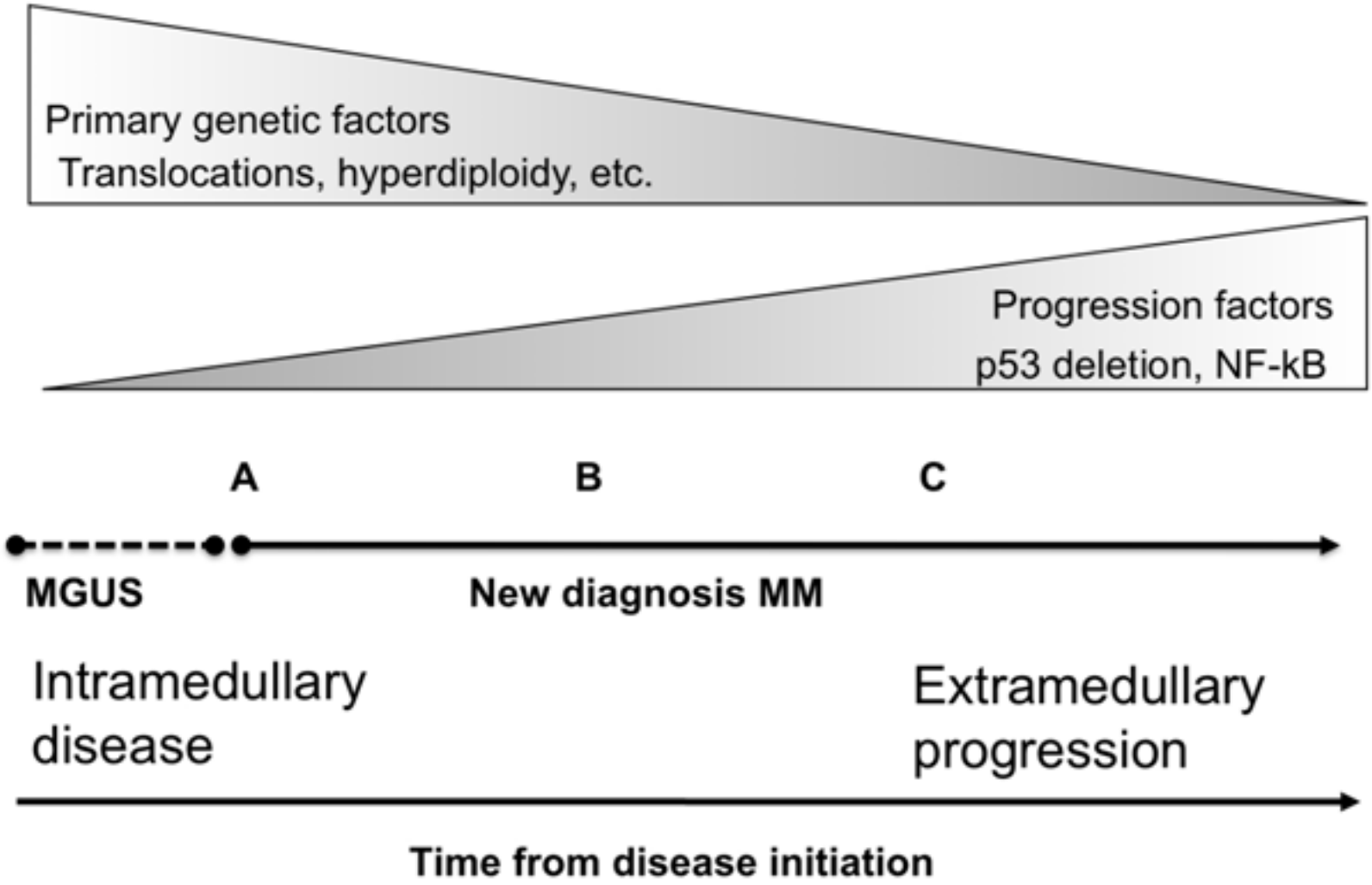
New Diagnosis MM



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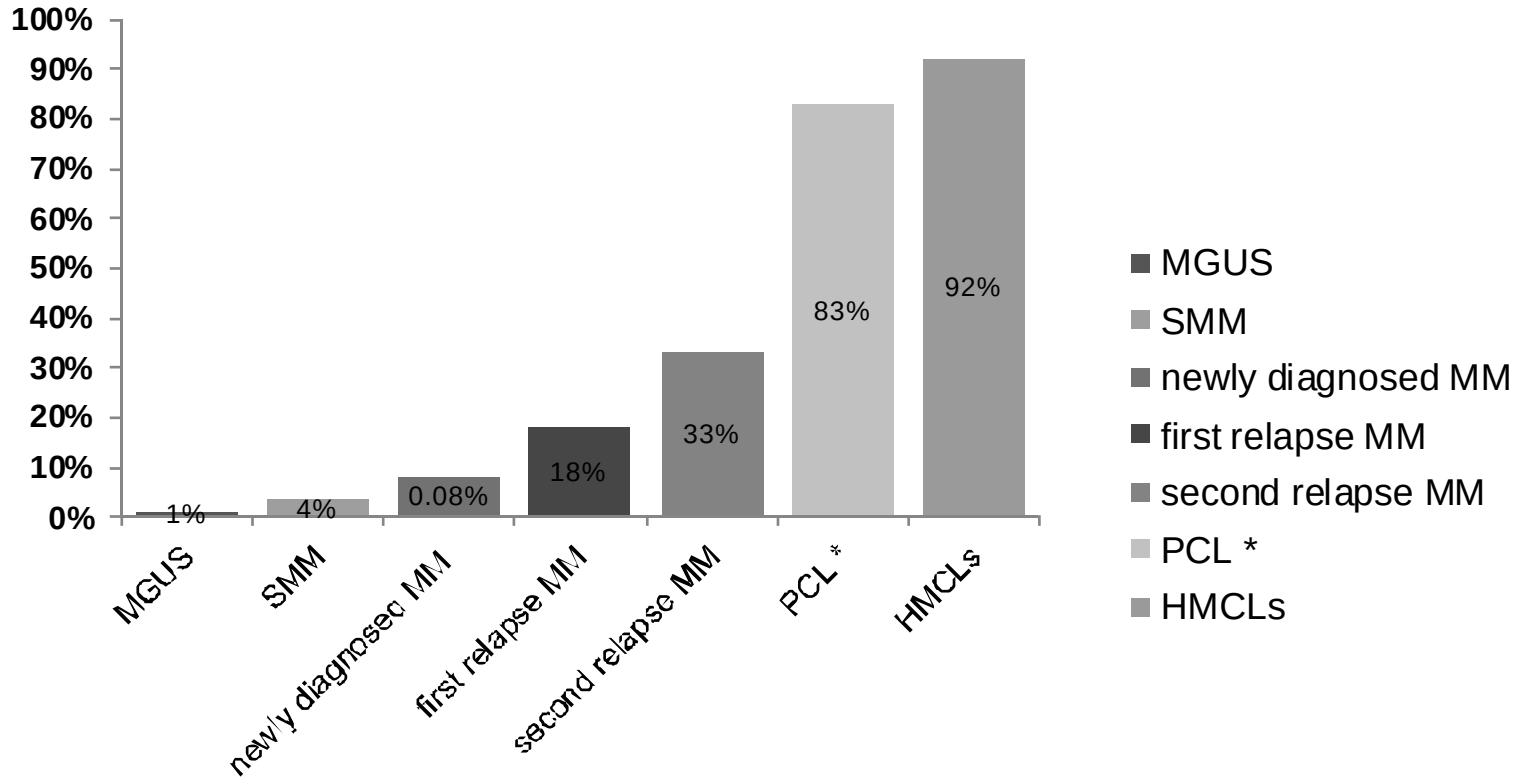
P53 deletion/mutation



Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)
p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

**Tiedemann et al. Leukemia. 2008; 22, 1044-1052*
Fonseca. Manuscript in preparation

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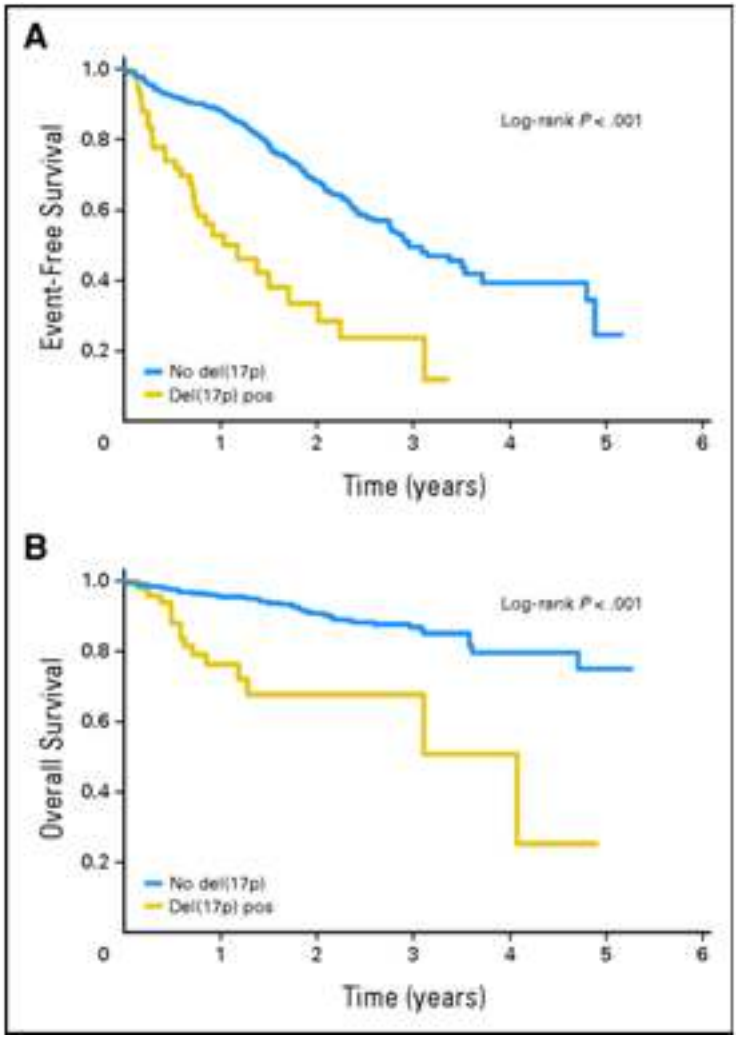
EFS and OS for -17p VAD vs VD



Avet-Loiseau H et al. JCO 2010;28:4630-4634

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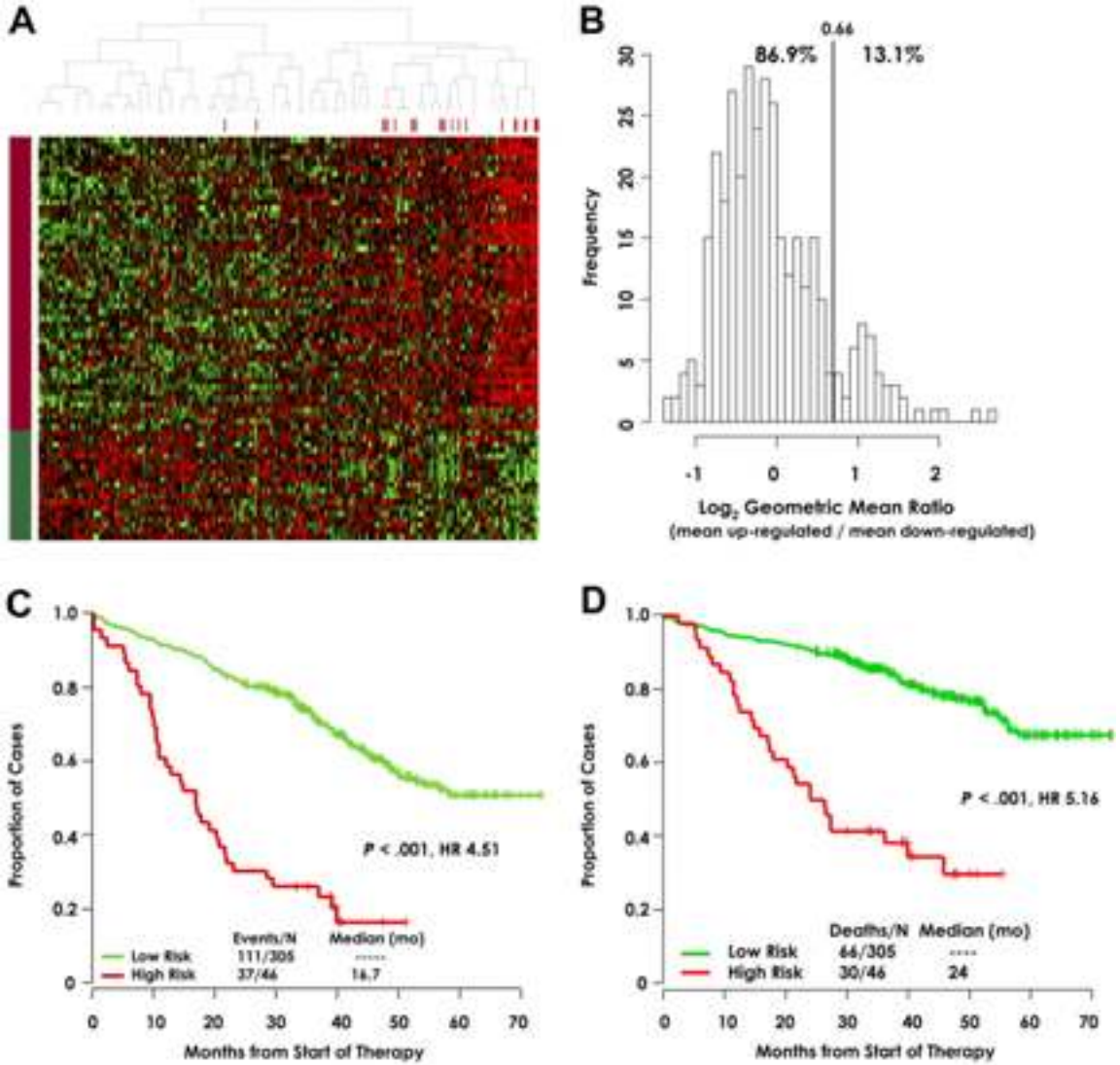
GEP signatures



Shaughnessy et al, Blood2007, 109(6), 2276-2284

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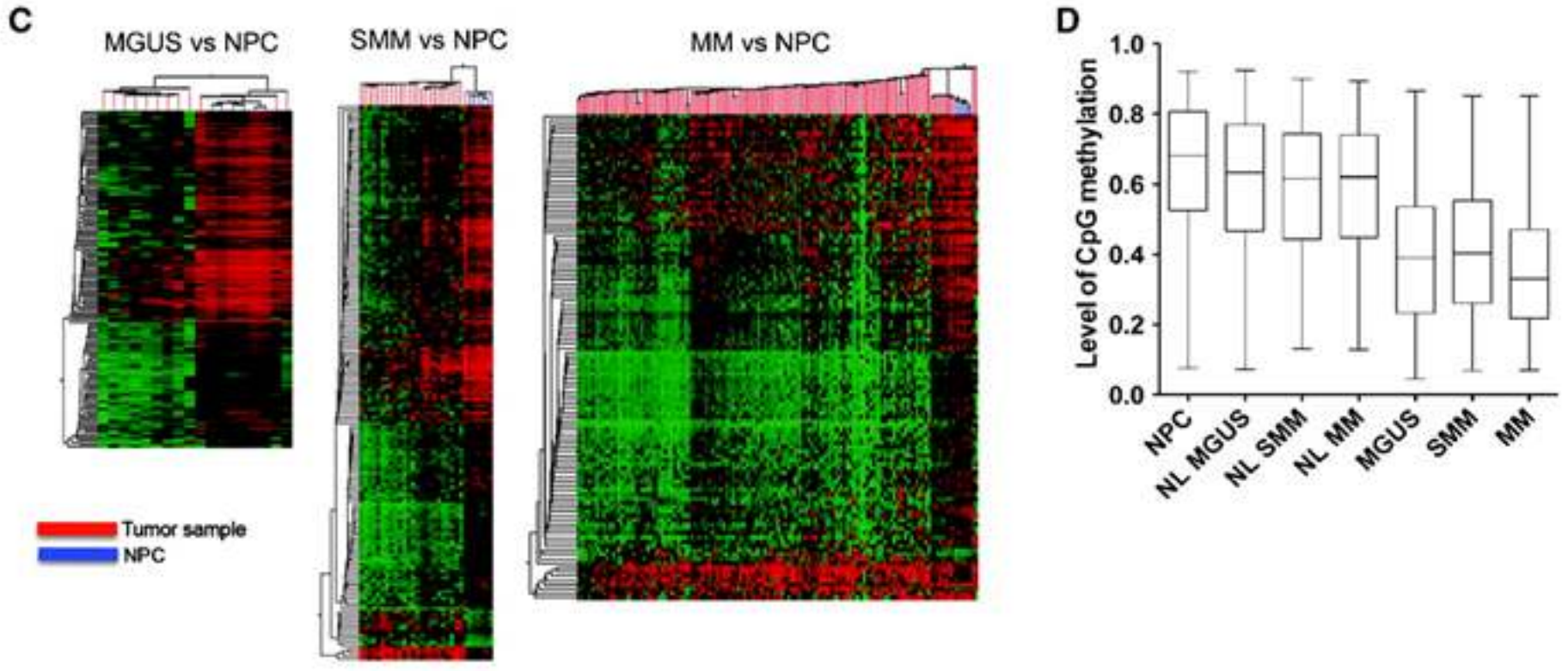
Total DML in Tumors and HMCL



Salhia B et al. Cancer Res 2010;70:6934-6944

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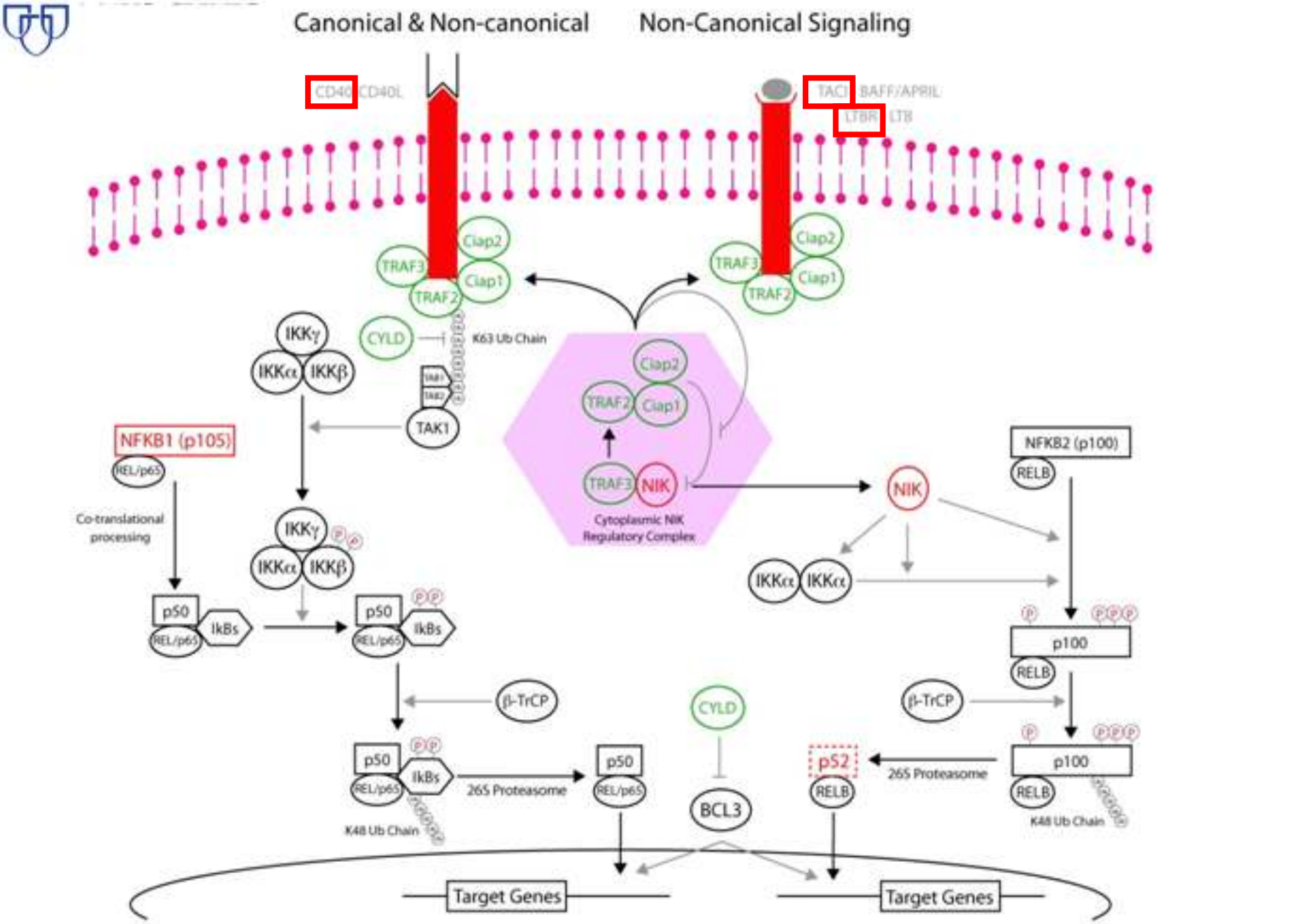
Initial genome sequencing and analysis of multiple myeloma

Michael A. Chapman[1]†, Michael S. Lawrence[1], Jonathan J. Keats[2,3], Kristian Cibulskis[1], Carrie Sougnez[1], Anna C. Schinzel[4], Christina L. Harview[1], Jean-Philippe Brunet[1], Gregory J. Ahmann[2,3], Mazhar Adli[1,5], Kenneth C. Anderson[3,4], Kristin G. Ardlie[1], Daniel Auclair[3,6], Angela Baker[7], P. Leif Bergsagel[2,3], Bradley E. Bernstein[1,5,8,9], Yotam Drier[1,10], Rafael Fonseca[2,3], Stacey B. Gabriel[1], Craig C. Hofmeister[3,11], Sundar Jagannath[3,12], Andrzej J. Jakubowiak[3,13], Amrita Krishnan[3,14], Joan Levy[3,6], Ted Liefeld[1], Sagar Lonial[3,15], Scott Mahan[1], Bunmi Mfuko[3,6], Stefano Monti[1], Louise M. Perkins[3,6], Robb Onofrio[1], Trevor J. Pugh[1], S. Vincent Rajkumar[3,16], Alex H. Ramos[1], David S. Siegel[3,17], Andrey Sivachenko[1], A. Keith Stewart[2,3], Suzanne Trudel[3,18], Ravi Vij[3,19], Douglas Voet[1], Wendy Winckler[1], Todd Zimmerman[3,20], John Carpten[7], Jeff Trent[7], William C. Hahn[1,4,8], Levi A. Garraway[1,4], Matthew Meyerson[1,4,8], Eric S. Lander[1,8,21], Gad Getz[1] & Todd R. Golub[1,4,8,9]

- CCND1 2%
- BRAF 4%
- DIS3 (RPP44) 11%
- FAM46C 13%
- XBP1 4%
- LRRK2 6%
- IRF 6%
- PRDM1 6%

- **Known**; ras (50%), NF-kB (37%), p53 (8%)
- **Protein translation 42%**
- **Histone modifying enzymes (lead HOXA9)**
- **Fibrin clot formation 16%**

Nature 24 March 2011, 471:467


Canonical & Non-canonical
Non-Canonical Signaling
CD40
CD40L
TACI
BAFF/APRIL
LTBR
LTB
Ciap2
TRAF3
Ciap1
TRAF2
CYLD
K63 Ub Chain
IKKγ
IKKα
IKKβ
TAB1
TAB2
TAK1
NFKB1 (p105)
REL/p65
Co-translational processing
p50
IkBs
Cytoplasmic NIK Regulatory Complex
NIK
NFKB2 (p100)
RELB
p100
β-TrCP
BCL3
p52
26S Proteasome
K48 Ub Chain
Target Genes

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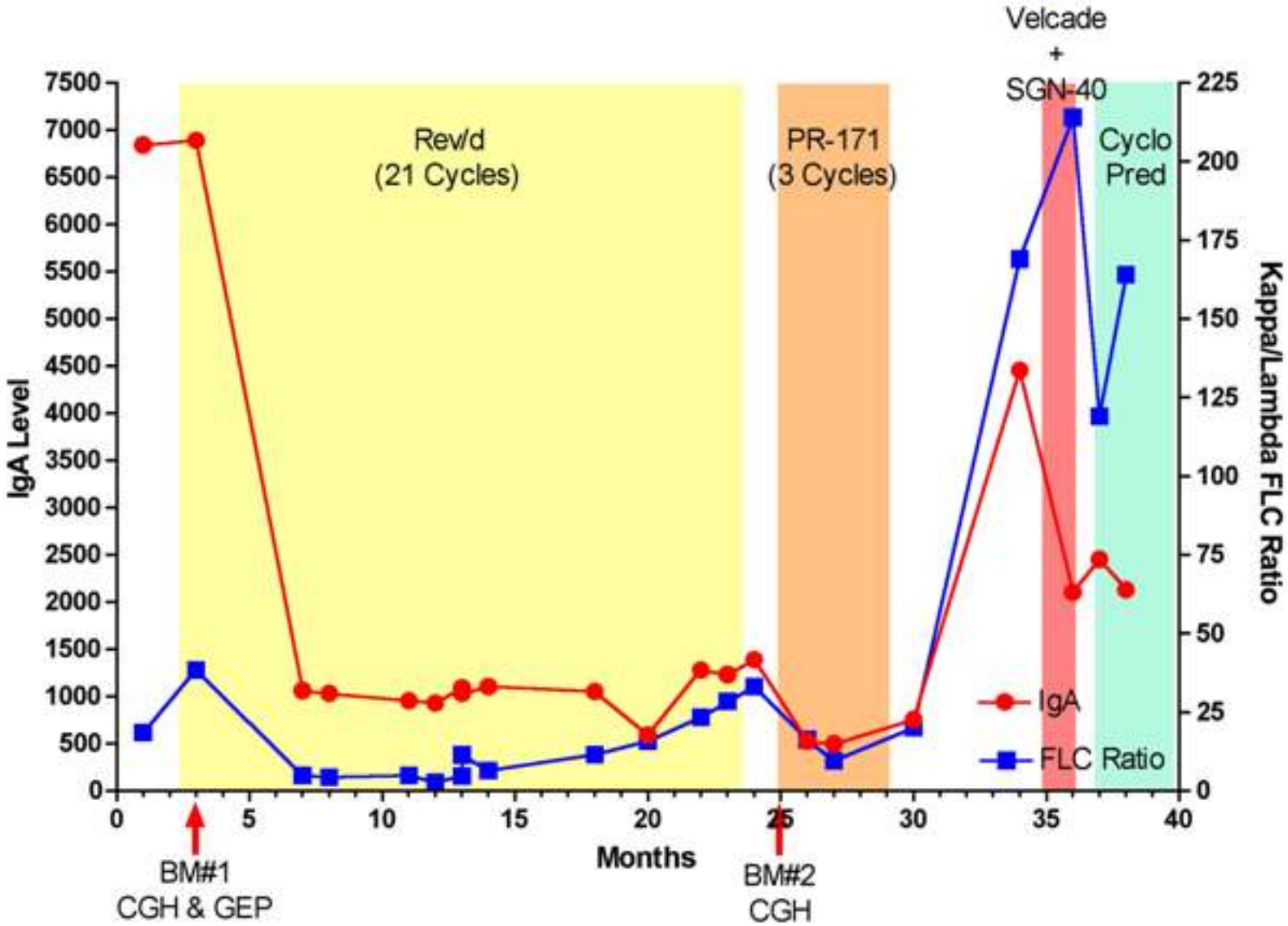
Clinical Course - Case Report



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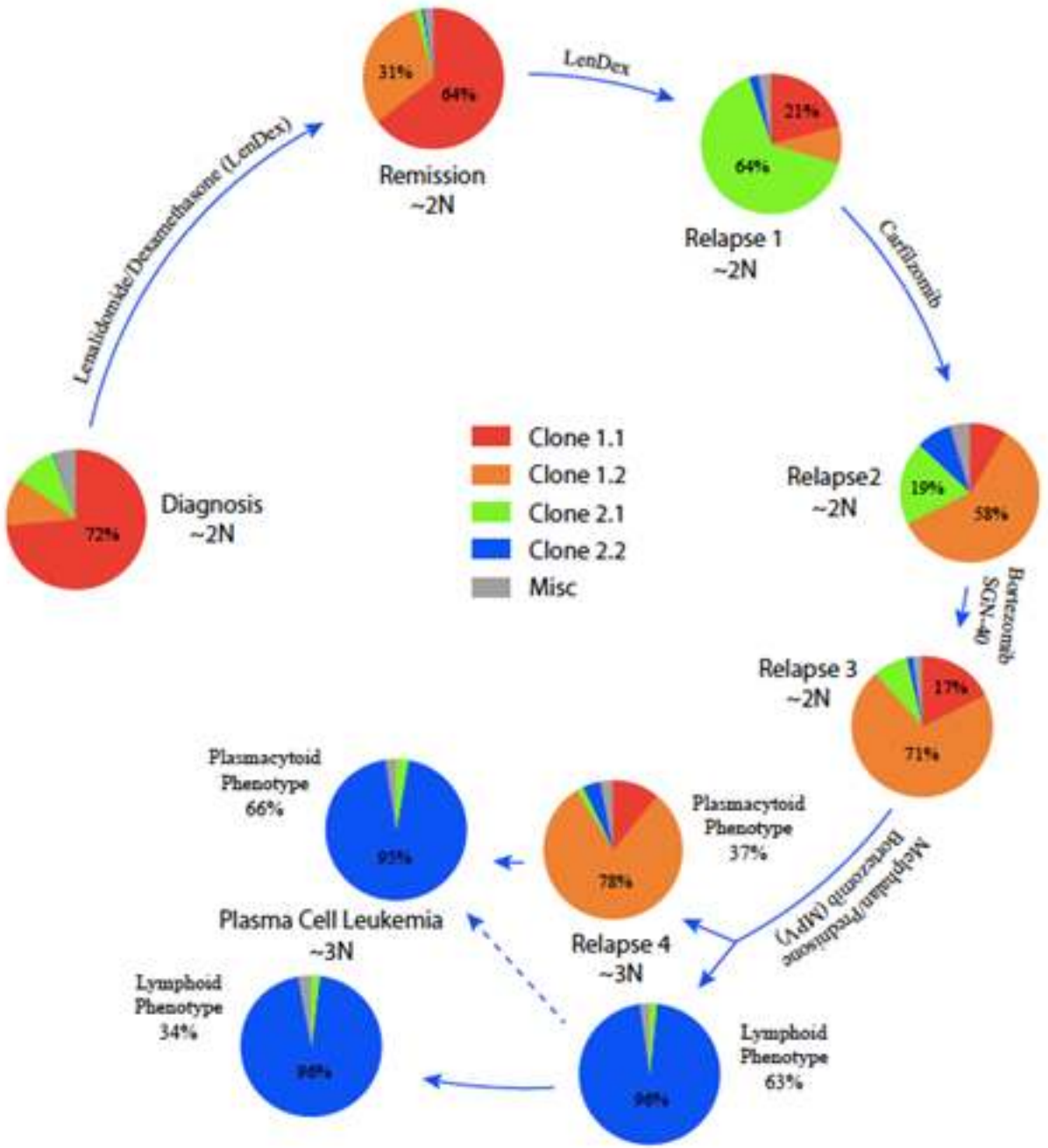
Remission
~2N
31%
64%
LenDex
Relapse 1
~2N
21%
64%
Carfilzomib
Relapse2
~2N
19%
58%
Bortezomib
SGN-40
Relapse 3
~2N
17%
71%
Melphalan/Prednisone
Bortezomib (MPV)
Relapse 4
~3N
Plasmacytoid
Phenotype
37%
78%
Plasmacytoid
Phenotype
66%
95%
Plasma Cell Leukemia
~3N
Lymphoid
Phenotype
34%
98%
Lymphoid
Phenotype
63%
98%
Diagnosis
~2N
72%
Lenalidomide/Dexamethasone (LenDex)
Clone 1.1
Clone 1.2
Clone 2.1
Clone 2.2
Misc

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Is myeloma like AP CML

CLINICAL TRIALS AND OBSERVATIONS

Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase

*Qian Jiang,[1] *Lan-Ping Xu,[1] Dai-Hong Liu,[1] Kai-Yan Liu,[1] Shan-Shan Chen,[1] Bin Jiang,[1] Hao Jiang,[1] Huan Chen,[1] Yu-Hong Chen,[1] Wei Han,[1] Xiao-Hui Zhang,[1] Yu Wang,[1] Ya-Zhen Qin,[1] Yan-Rong Liu,[1] Yue-Yun Lai,[1] and Xiao-Jun Huang[1]

[1]Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China

The relative merits of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and imatinib for chronic myelogenous leukemia in the accelerated phase (AP-CML) have not previously been evaluated. This cohort study was designed to compare the outcomes of imatinib (n = 87) versus allo-HSCT (n = 45) for AP-CML. A multivariate analysis of the total population revealed that a CML duration ≥ 12 months, hemoglobin < 100 g/L, and peripheral blood blasts ≥ 5% were independent adverse prognostic factors for both overall survival (OS) and progression-free survival (PFS). Both treatments resulted in similar survival in low-risk (no factor) patients, with 6-year event-free survival (EFS), OS, and PFS rates of more than 80.0%. Intermediate-risk (any factor) patients showed no difference in EFS and OS, but 6-year PFS rates were 55.7% versus 92.9% (P = .047) with imatinib versus allo-HSCT, respectively. Among high-risk (at least 2 factors) patients, imatinib was by far inferior to allo-HSCT, with 5-year EFS, OS, and PFS rates of 9.3% versus 66.7% (P = .034), 17.7% versus 100% (P = .008), and 18.8% versus 100% (P = .006), respectively. We conclude that allo-HSCT confers significant survival advantages for high- and intermediate-risk patients with AP-CML compared with imatinib treatment; however, the outcomes of the 2 therapies are equally good in low-risk patients. All trials were registered with the Chinese Clinical Trial Registry (www.chictr.org) as CHICTR-TNC-10000955. (*Blood.* 2011;117(11): 3032-3040)

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So many, many, many, many MM!

- **Ultimately all will be…**
  - An “N of 1”
  - All classifiers will be global approximations
  - How many “buckets” to use is arbitrary and defined by **clinical utilitarian needs**

N of 1

Acknowledgements

Mayo Clinic

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Leif Bergsagel

Marta Chesi

Phil Greipp

Robert Kyle

SV Rajkumar

Dysproteinemia Group

Joe Mikhael

Craig Reeder

Gordon Dewald

Syed Jalal

Rhett Ketterling

Mayo Clinic

Esteban Braggio

Travis Henry

Samar Issa

Angela Mayo

Jacy Spong

NUS

Wee Joo Chng

TGEN

Jeff Trent

John Carpten

Mike Barrett

Laboratory

Greg Ahmann

Scott Van Wier

Tammy Price-Troska

Rachel Hagerty

Kim Henderson

Laboratory