Four genes predict high risk of progression from smoldering to symptomatic multiple myeloma (SWOG S0120)

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Supplemental Table 1: Top 40 probesets associated with TTT

Probeset	Gene	Location	HR	p-value	q-value
201890_at	RRM2	chr2p25-p24	2.650446	1.38E-08	0.000661
218585_s_at	DTL	chr1q32	2.62824	3.41E-08	0.000814
218073_s_at	TMEM48	chr1p32.3	4.841083	8.20E-08	0.001057
219918_s_at	ASPM	chr1q31	2.293548	8.85E-08	0.001057
204240_s_at	SMC2	chr9q31.1	5.1923	6.72E-07	0.006422
209773_s_at	RRM2	chr2p25-p24	2.418279	9.25E-07	0.007372
202589_at	TYMS	chr18p11.32	2.322381	1.12E-06	0.00765
200896_x_at	HDGF	chr1q21-q23	4.200135	2.36E-06	0.014096
202705_at	CCNB2	chr15q22.2	2.220905	2.69E-06	0.01428
212539_at	CHD1L	chr1q12	4.754101	3.24E-06	0.015188
203755_at	BUB1B	chr15q15	2.846589	3.51E-06	0.015188
218039_at	NUSAP1	chr15q15.1	2.762533	3.81E-06	0.015188
213008_at	FANCI	chr15q26.1	1.616492	5.75E-06	0.021131
222680_s_at	DTL	chr1q32	2.150436	6.66E-06	0.022729
225625_at	ALKBH2	chr12q24.11	4.633574	8.77E-06	0.026344
213079_at	TSR2	chrXp11.22	0.198068	9.17E-06	0.026344
1554768_a_at	MAD2L1	chr4q27	3.002631	9.61E-06	0.026344
220489_s_at	SERINC2	chr1p35.1	0.556833	1.10E-05	0.026344
226350_at	CHML	chr1q42-qter	2.236901	1.10E-05	0.026344
223681_s_at	INADL	chr1p31.3	0.631531	1.12E-05	0.026344
204170_s_at	CKS2	chr9q22	1.960739	1.16E-05	0.026344
212639_x_at	LOC100288366 /// TUBA1A /// TUBA1B	chr12q13.12	6.882019	1.23E-05	0.026472
202534_x_at	DHFR	chr5q11.2-q13.2	4.350659	1.30E-05	0.026472
208938_at	PRCC	chr1q21.1	3.599987	1.33E-05	0.026472
208114_s_at	ISG20L2	chr1q23.1	4.214643	1.42E-05	0.027112
202613_at	CTPS1	chr1p34.1	3.755017	1.53E-05	0.027374
212502_at	ADO	chr10q21.3	3.376319	1.55E-05	0.027374
222606_at	ZWILCH	chr15q22.31	3.893446	1.95E-05	0.03245
217900_at	IARS2	chr1q41	3.433162	2.02E-05	0.03245
211071_s_at	MLLT11	chr1q21	2.802617	2.04E-05	0.03245
216484_x_at	HDGF	chr1q21-q23	4.528852	2.16E-05	0.033313
231697_s_at	---	---	0.571499	2.42E-05	0.035506
218009_s_at	PRC1	chr15q26.1	1.917865	2.45E-05	0.035506
1562432_at	---	---	0.593852	2.65E-05	0.037276
201663_s_at	SMC4	chr3q26.1	3.287581	2.86E-05	0.039088
209044_x_at	SF3B4	chr1q21.2	3.439803	3.27E-05	0.043451
219148_at	PBK	chr8p21.2	2.667507	3.37E-05	0.043492
224459_at	L2HGDH	chr14q21.3	0.617417	3.58E-05	0.04432

218678_at	NES	chr1q23.1	1.269046	3.62E-05	0.04432
203362_s_at	MAD2L1	chr4q27	2.059193	3.82E-05	0.04568

Supplemental Table 2: Pathways involved by various genes represented by the top 40 probesets

Pathway	**Genes**
Cell cycle checkpoint control/apoptosis	BUB1B, MAD2L1 (which encodes MAD2), PRCC, ZWILCH, MLLT11, ASPM, PRC1, NES
DNA replication/repair	DTL, SMC2, SMC4, CHD1L, FANCI
Cellular proliferation	HDGF, NES
Biosynthetic pathway/metabolism	DHFR, TYMS, RRM2, CTPS1, ADO, L2HGDH
Cellular assembly/organization	NUSAP, SMC4, INADL
RNA transport/processing	TMEM48 (NDC1), TSR2, IARS2, S3B4
IL-6 signaling	PBK

Supplemental Table 3: Univariate Cox regression for TTT

			Time to Therapy for MM	
	Variable	**n/N (%)**	**HR (95% CI)**	**P-value**
Univariate	Age >= 65 yr	45/105 (43%)	2.27 (1.23, 4.17)	0.008
	Female	47/105 (45%)	0.77 (0.42, 1.42)	0.405
	White	91/105 (87%)	4.02 (0.97, 16.62)	0.055
	Albumin < 3.5 g/dL	20/105 (19%)	3.68 (1.94, 6.96)	<.001
	B2M >= 3.5 mg/L	26/104 (25%)	1.30 (0.65, 2.60)	0.453
	B2M > 5.5 mg/L	6/104 (6%)	0.91 (0.22, 3.77)	0.897
	Creatinine >= 2 mg/dL	3/105 (3%)	0.85 (0.12, 6.20)	0.874
	Hb < 10 g/dL	2/105 (2%)	1.18 (0.16, 8.65)	0.867
	M Protein >= 3 g/dL	24/104 (23%)	5.13 (2.77, 9.51)	<.001
	Excess Kappa Free Light Chains	62/105 (59%)	0.95 (0.52, 1.76)	0.880
	Excess Lambda Free Light Chains	28/105 (27%)	1.93 (1.03, 3.62)	0.042
	Normal FLC Ratio	15/105 (14%)	0.25 (0.06, 1.02)	0.052
	Involved light chain > 25 (mg/dL)	27/90 (30%)	1.98 (1.06, 3.68)	0.032
	Involved/uninvolved ratio > 8	58/90 (64%)	2.30 (1.09, 4.82)	0.028
	Involved/uninvolved ratio > 100	17/90 (19%)	1.53 (0.75, 3.12)	0.243
	BMPC >= 10%	90/104 (87%)	8.28 (1.14, 60.24)	0.037
	Cytogenetic abnormalities	16/103 (16%)	1.52 (0.70, 3.28)	0.286
	GEP CD-1 subgroup	2/105 (2%)	0.00 (0.00, .)	0.987
	GEP CD-2 subgroup	23/105 (22%)	0.54 (0.23, 1.29)	0.165
	GEP HY subgroup	29/105 (28%)	0.85 (0.43, 1.68)	0.632
	GEP LB subgroup	25/105 (24%)	1.06 (0.53, 2.10)	0.868
	GEP MF subgroup	11/105 (10%)	0.96 (0.34, 2.68)	0.933
	GEP MS subgroup	12/105 (11%)	1.78 (0.83, 3.85)	0.140
	GEP PR subgroup	3/105 (3%)	9.36 (2.66, 32.91)	<.001
	GEP 70-gene risk > -0.26	35/105 (33%)	3.35 (1.83, 6.15)	<.001
	GEP 4-gene score >= 9.28	14/105 (13%)	11.26 (5.51, 22.99)	<.001
	GEP proliferation index > -2.73	50/105 (48%)	2.78 (1.48, 5.22)	0.001
	GEP centrosome index > 2.76	17/105 (16%)	3.15 (1.60, 6.20)	<.001
	GEP poly PC > 11.6	30/105 (29%)	0.22 (0.08, 0.60)	0.003
	MRI FL >= 1	11/64 (17%)	2.59 (1.12, 6.00)	0.026
	MRI FL >= 2	3/64 (5%)	2.08 (0.48, 8.92)	0.326
	Serum M-protein increase from baseline by 1 g/dL**		21.14 (10.32, 43.27)	<.001

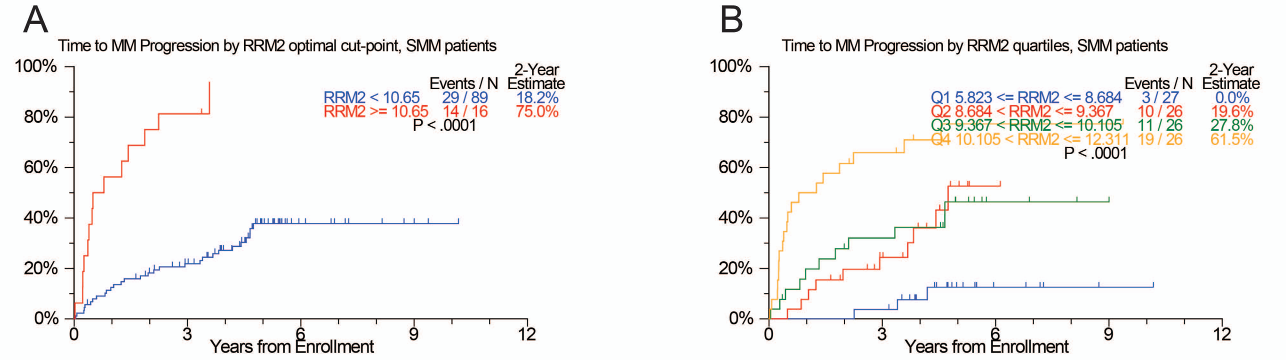
HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Cox Regression.

**Denotes a time-dependent variable.

Supplemental Table 4: Comparison of existing stratification models for SMM

Dataset	**Type of data**	**Variables**	**2-year risk for highest risk group**
Heidelberg	Retrospective	t(4;14), del17, 1q21 gain, hyperdiploidy, M protein > 2 g/dL	40%
PETHEMA	Retrospective	>95% aberrant/bone marrow plasma cells, DNA aneuploidy and immunoparesis	44%
Mayo – FISH	Retrospective	Del17p, or t(4;14)	45%
Mayo – clinical, 2008	Retrospective	BMPC ≥ 10, M protein ≥ 30 g/L, and involved FLC/uninvolved FLC ≥ 8	52%
Mayo – clinical, 2012	Retrospective	Serum involved/uninvolved FLC ratio ≥ 100	72%
SWOG – GEP + clinical	Prospective	GEP70 > -0.26, serum M spike ≥ 3 g/dL, and involved SFLC > 25 mg/dL	67%
Penn – clinical, 2014	Retrospective	BMPC > 40% + sFLC ratio > 50 + albumin < 3.5 g/dL	81%
Mayo – BMPC, 2011	Retrospective	BMPC > 60%	95%
Heidelberg – MRI, 2010	Retrospective	>1 focal lesion on whole body MRI	70%
SWOG – GEP4	Prospective	GEP4 > 9.28	86%

Supplemental Figure 1: TTT by RRM2 optimal cut-point (A) and quartiles (B)



Supplemental Table 5: Overlap with previously reported GEP-based models in CMM

Model	**Overlap genes**
UAMS GEP70	ASPM
HOVON-65 – EMC92	FANCI, DTL, DHFR
CIN – 6 different tumors	PRC1, MAD2L1, CCNB2, CKS2, CTPS, HDGF, ZWILCH, HDGF
CIN – sarcoma study	RRM2, ASPM, SMC2, CCNB2, BUB1B, FANCI, CKS2, PRC1, PBK, MAD2L1
CINGECS – MM derived and prognostic	RRM2, ASPM, SMC2, TYMS, CCNB2, BUB1B, NUSAP1, FANCI, DTL, CKS2, ZWILCH, PRC1, PBK, MAD2L1