

Supplemental Digital Content, Containing 5 Tables and 2 Figures

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<i>Supplemental Table 1: MiQE Context Sequences for Target and Reference Gene Probes</i>	
Gene	MiQE Context Sequence of Probe (5' to 3')
<i>RREB1</i>	GGATAAGATGATAATTTCTTAAATAGACATTTTCCTTTTTTCTTTGT GCTTCATGGTGGAGCTGTCATCTGGTCCTTGGTATTACAGGATGT GGTTGATGAAGGTTTCCAATATGGTTTCAGG
<i>CDKN2A</i>	TTCCTTGGCTTCCCAAGCCCCAGGGCGTCGCCAGGAGGAGGTC TGTGATTACAAACCCCTTCTGAAAACCTCCCAGGAAGCCTCCCCT TTTTCCGGAGAATCGAAGCGCTACCTGATTCCAA
<i>MYC</i>	ACAATGAAAAGGCCCCCAAGGTAGTTATCCTTAAAAAAGCCACAG CATACATCCTGTCCGTCCAAGCAGAGGAGCAAAGCTCATTTCTG AAGAGGACTTGTTGCGGAAACGACGAGAACAGT
<i>MYB</i>	TGTTTCCTCCTCCTCCTTCTCCTCCTCCTCCGTGACCTCCTCCTCC TCTTTCTCCTGAGAACTTCGCCCCAGCGGTGCGGAGCGCCGCTG CGCAGCCGGGGAGGGACGCAGGCAGGCGGCGG
<i>EIF2C1</i>	GAGGGCTACTACCACCCGCTGGGGGGTGGGCGCGAGGTCTGGT TCGGCTTTCACCAGTCTGTGCGCCCTGCCATGTGGAAGATGATGC TCAACATTGATGGTGAGTGGGGAGAGCTATGGAGC
<i>THNSL2</i>	GTGGGGTTTTGTCATCTTTCCCTACATCCCCCCCCACACCTCAT CTTTCTGACCTGGGACCCTTCAGCTTTCAGAGGCAGTGACATCCG TGTCAGTGTCGGATGAAGCCATCACCCAGACCA
<i>EFTUD2</i>	CTCTTTTTCACTGGGGGAGAACAGAGTAAGGGACTGGTGGTAGCTGGGGA GAGGACTTGGAGTAAATGGCTGGAAATCAAAGTGCTCTGGCCCCCTACTCC AGGGCAAGGAAGATTCTTAGGG
<i>SLAIN2</i>	TCCACTCAAAAATTGGTTTTTCTTTGCCATCCCACAGTACCTTCTCCAGGC AAATTCGTTCCCCTGCAGCACCATCTCCTTTGGCTCTTCGGCAACCAGTG AAAGCATTTAGTAACCATGGC
<i>RPPH1</i>	TTTTTTTCCAAAATGGGCGGAGGAGAGTAGTCTGAATTGGGTTATGAGGT

	CCCCTGCGGGGTACCTCACCTCAGCCATTGAACTCACTTCGCTGGCCGTGA GTCTGTTCCAAGCTCCGGCAA
<i>RPLP0</i>	CAGACCCTGTGTCAAAAAGGAAAAAAAAAATTACAAAATTAAGAGTCCAGAG ACTTTTAAAGAAGTAAGCCTTTATTTCTTGTGTTTGCAAATAAACTGGCT AAGTTGGTTGCTTTTTGGTGA
<i>LIPI</i>	CTCAAATTGAACAGTGCATTATAAAAGACTGATTGCATTGTTTCATTTACAA GTCCATTAATTCACAAGCAAGTGCATTTGATGGAAGAAGGCATCTTATGTG TTCTTTGGTGTACATGTGTT
<p>Note: “MiQE” = Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE); “<i>RREB1</i>” = Ras-responsive binding element protein 1; “<i>CDKN2A</i>” = cyclin-dependent kinase inhibitor 2A; “<i>EIF2C1</i>” = Eukaryotic Translation Initiation Factor 2C; “<i>THNSL2</i>” = threonine synthase like 2; “<i>EFTUD2</i>” = Elongation Factor Tu GTP Binding Domain Containing 2; “<i>SLAIN2</i>” = SLAIN Motif Family Member 2; “<i>RPPH1</i>” = ribonuclease P RNA component H1; “<i>RPLP0</i>” = Ribosomal Protein Lateral Stalk Subunit P0; “<i>LIPI</i>” = lipase 1.</p>	

Supplemental Table 2: Expanded Demographic, Histological, and Clinicopathologic Data for All Patients

ID	Age at Biopsy	Sex	Lesion Classification	Lesion Location	Lesion Size (cm)	BD (mm) / Ulceration	Final Diagnosis
1	62	M	Metastatic Melanoma	Lymph Node	0.2	-	Metastatic melanoma
2	5	F	Borderline Lesion	-	-	-	Atypical Spitz Tumor
3	47	F	Borderline Lesion	Upper Extremity	1.3	-	MELTUMP
4	39	M	Borderline Lesion	Upper Extremity	1.1	-	Combined epithelioid melanocytoma associated with a nevus
5	38	F	Borderline Lesion	Trunk	0.6	-	Atypical melanocytic nevus
6	75	M	Benign Nevus	Trunk	0.7	-	Compound melanocytic nevus
7	32	F	Borderline Lesion	Upper Extremity	0.9	-	Atypical Spitz tumor
8	60	F	Borderline Lesion	Upper Extremity	0.8	-	Predominantly intradermal melanocytic nevus w/ sclerosing features and mitotic activity
9	46	F	Benign Nevus	Head/Neck	1.5	-	BAP1-deficient nevus
10	18	F	Benign Nevus	Trunk	0.6	-	Spitz nevus
11	74	M	Melanoma	Head/Neck	1.6	3.0 / Yes	Superficial spreading melanoma
12	74	M	Melanoma	Head/Neck	2.0	0.0 / No	Melanoma in situ
13	82	F	Borderline Lesion	Upper Extremity	0.9	-	Atypical intraepidermal melanocytic proliferation
14	44	F	Borderline Lesion	Head/Neck	-	-	Atypical melanocytic nevus
15	68	F	Melanoma	Trunk	1.5	0.7 / No	Melanoma, not otherwise specified
16	63	M	Melanoma	Trunk	1.3	0.3 / No	Superficial Spreading Melanoma
17	80	M	Melanoma	Head/Neck	1.6	0.7 / No	Nevoid Melanoma
18	70	M	Melanoma	Trunk	1.4	0.7 / No	Superficial Spreading Melanoma
19	86	M	Metastatic Melanoma	Cutaneous	0.4	-	Metastatic Melanoma
20	86	M	Metastatic Melanoma	Brain	1.7	-	Metastatic Melanoma
21*	64	M	Metastatic Melanoma	Liver	2.2	-	Metastatic Melanoma
22*	64	M	Metastatic Melanoma	Liver	2.7	-	Metastatic Melanoma
23	51	M	Metastatic Melanoma	Lymph Node	3.2	-	Metastatic Melanoma
24^	53	F	Metastatic Melanoma	Gastrointestinal	4.7	-	Metastatic Melanoma
25^	53	F	Metastatic Melanoma	Gastrointestinal	4.7	-	Metastatic Melanoma
26^	53	F	Metastatic Melanoma	Gastrointestinal	4.7	-	Metastatic Melanoma
27	63	M	Melanoma	Lower Extremity	0.7	1.6 / No	Nodular Melanoma
28	55	M	Melanoma	Head/Neck	0.7	1.6 / No	Nevoid Melanoma
29	63	M	Melanoma	Head/Neck	0.8	2.75 / No	Mixed (Desmoplastic and Nodular)
30	12	M	Borderline Lesion	Head/Neck	0.7	-	Atypical Spitz Tumor

31	15	M	Borderline Lesion	Trunk	1.0	-	Atypical Spitz Tumor
32	33	F	Borderline Lesion	Upper Extremity	0.9	-	Atypical melanocytic nevus
33	47	M	Melanoma	Upper Extremity	0.9	2.1 / No	Nevoid Melanoma
34	81	F	Metastatic Melanoma	Breast	0.9	-	Metastatic Melanoma
35 [#]	56	M	Metastatic Melanoma	Lymph Node	3.5	-	Metastatic Melanoma
36 [#]	56	M	Metastatic Melanoma	Lymph Node	3.5	-	Metastatic Melanoma
37 [%]	70	F	Metastatic Melanoma	Gastrointestinal	14.8	-	Metastatic Melanoma
38 [%]	70	F	Metastatic Melanoma	Gastrointestinal	14.8	-	Metastatic Melanoma
39 ^{&}	66	M	Metastatic Melanoma	Cutaneous	1.3	-	Metastatic Melanoma
40 ^{&}	66	M	Metastatic Melanoma	Cutaneous	1.3	-	Metastatic Melanoma
41 ^{&}	66	M	Metastatic Melanoma	Cutaneous	1.3	-	Metastatic Melanoma
42	73	M	Melanoma	Head/Neck	1.5	4.1 / Yes	Melanoma, not otherwise specified
43	96	M	Melanoma	Special Site	0.3	2.7 / Yes	Not Otherwise Specified
44 [@]	82	F	Melanoma	Special Site	1.3	4.8 / Yes	Nevoid Melanoma
45 [@]	82	F	Melanoma	Special Site	1.3	4.8 / Yes	Nevoid Melanoma
46	82	M	Melanoma	Head/Neck	3.0	4.9 / No	Not Otherwise Specified
47	96	M	Melanoma	Upper Extremity	10.3	9.8 / Yes	Nodular Melanoma
48	58	M	Melanoma	Trunk	1.6	4.2 / Yes	Nodular melanoma
49	65	M	Melanoma	Head/Neck	1.2	0.2 / No	Lentigo Maligna Melanoma
50	79	M	Melanoma	Trunk	2.8	0.4 / No	Lentigo Maligna Melanoma
51 ^{**}	71	M	Melanoma	Head/Neck	6.7	6.4 / Yes	Spindle Cell Melanoma
52 ^{**}	71	M	Melanoma	Head/Neck	6.7	6.4 / Yes	Spindle Cell Melanoma
53	84	M	Melanoma	Head/Neck	0.4	1.2 / No	Superficial Spreading Melanoma
54	69	M	Melanoma	Head/Neck	0.7	1.2 / No	Nevoid Melanoma
55	76	M	Melanoma	Trunk	1.8	2.5 / Yes	Nodular melanoma
56	59	M	Melanoma	Trunk	1.6	5.0 / Yes	Nodular Melanoma
57	65	M	Melanoma	Trunk	1.9	0.9 / No	Superficial Spreading Melanoma
58	69	M	Melanoma	Head/Neck	5.5	1.5 / Yes	Mixed (Spindle and Desmoplastic)
59	67	F	Melanoma	Upper Extremity	1.1	1.3 / No	Not Otherwise Specified
60	63	M	Melanoma	Trunk	1.1	3.2 / No	Nodular Melanoma
61	62	M	Melanoma	Upper Extremity	2.5	3.3 / No	Nodular Melanoma
62	68	M	Melanoma	Lower Extremity	1.4	3.8 / No	Not Otherwise Specified
63	44	M	Melanoma	Head/Neck	4.6	16 / No	Melanoma Arising in Blue Nevus
64	74	M	Melanoma	Trunk	2.1	2.9 / No	Superficial Spreading Melanoma
65	51	M	Metastatic Melanoma	Lymph Node	3.2	-	Metastatic Melanoma

Note: *, ^, #, %, &, @ and ** - Different sections from the same patient's tumor; BD = Breslow Depth; cm = centimeters; mm = millimeters; ID = case identification number; M = male; F = female; "-" = not recorded; "METLUMP" = melanocytic tumor of uncertain malignant potential; "BAP1" = BRCA1-associated protein 1

Supplemental Table 3: Histopathologic Characteristics of All Cases

ID	Lesion Classification	Lymph Node-Like Inflammation	Prominent Background Nevus	Expansile, Nodular Growth with Epithelioid Melanocytes	Sheetlike Growth	Necrosis	Hemorrhage	Epithelioid Melanocytes with Abundant Cytoplasm
1	Metastatic	y	n	n	y	y	y	y
2	Borderline	n	n	n	n	n	n	n
3	Borderline	n	n	n	n	n	n	n
4	Borderline	n	n	n	n	n	n	n
5	Borderline	n	n	n	n	n	n	n
6	Benign	n	n	n	n	n	n	n
7	Borderline	y	n	n	n	n	n	y
8	Borderline	n	n	n	n	n	n	n
9	Benign	n	n	y	n	n	n	n
10	Benign	n	n	n	n	n	n	n
11	Melanoma	y	n	n	y	y	y	n
12	Melanoma	n	n	n	n	n	n	n
13	Borderline	n	n	n	n	n	n	n
14	Borderline	n/a	n/a	n/a	n/a	n/a	n/a	n/a
15	Melanoma	n	n	n	n	n	n	n
16	Melanoma	n	n	n	n	n	n	n
17	Melanoma	n	n	n	n	n	n	n
18	Melanoma	n	y	y	n	n	n	n
19	Metastatic	n	n	y	n	y	n	n
20	Metastatic	n	n	n	n	y	y	y
21	Metastatic	n	n	y	n	y	n	n
22	Metastatic	n	n	y	n	y	y	n
23	Metastatic	y	n	y	n	y	n	y
24	Metastatic	n	n	n	n	y	n	y
25	Metastatic	y	n	y	n	y	y	n
26	Metastatic	n	n	n	y	y	n	y
27	Melanoma	n	n	y	n	n	n	y
28	Melanoma	n	y	y	n	n	n	n
29	Melanoma	n	y	n	n	n	n	n
30	Borderline	n	y	n	n	n	n	y
31	Borderline	n	y	y	n	n	n	n
32	Borderline	n	n	n	n	n	n	y
33	Melanoma	n	y	y	y	n	n	y
34	Metastatic	n	n	n	y	y	n	y
35	Metastatic	y	n	y	y	y	y	y
36	Metastatic	y	n	y	y	y	y	y

37	Metastatic	n	n	n	y	n	n	y
38	Metastatic	n	n	n	y	n	n	y
39	Metastatic	n	y	y	n	n	y	n
40	Metastatic	n	n	y	n	n	n	n
41	Metastatic	n	n	y	y	n	y	n
42	Melanoma	n	n	y	n	n	n	n
43	Melanoma	n	n	n	y	n	n	n
44	Melanoma	n	n	n	y	y	n	n
45	Melanoma	n	n	n	y	y	y	n
46	Melanoma	n	n	y	n	n	y	y
47	Melanoma	n	n	y	n	n	y	n
48	Melanoma	n	n	y	y	y	n	n
49	Melanoma	n	n	n	n	n	n	n
50	Melanoma	y	n	n	n	n	n	n
51	Melanoma	n	n	n	n	y	y	y
52	Melanoma	n	n	n	n	y	y	n
53	Melanoma	n	n	n	y	n	n	n
54	Melanoma	n	y	y	n	n	n	n
55	Melanoma	n	n	y	y	y	n	y
56	Melanoma	n	n	y	n	n	n	y
57	Melanoma	n	y	n	n	n	n	n
58	Melanoma	n	n	n	y	y	n	n
59	Melanoma	n	n	n	n	n	n	n
60	Melanoma	n	n	y	n	n	n	n
61	Melanoma	n	n	y	n	n	n	n
62	Melanoma	n	n	y	n	y	n	y
63	Melanoma	n	n	y	y	y	y	n
64	Melanoma	n	n	y	y	n	n	y
65	Metastatic	y	n	y		y	n	y

Note: "y" = present; "n" = absent. "n/a" = referral case returned to outside institution prior to histologic review; "ID" = case identification number

Supplemental Table 4: Summary of ddPCR, CMA, and Lesion Classification Data for All Samples

ID	Lesion Classification	MYC Gain ^a Median ddPCR (+/-)	MYC Gain CMA (+/-)	MYB Loss ^b Median ddPCR (+/-)	MYB Loss CMA (+/-)	RREB1 Gain ^c Median ddPCR (+/-)	RREB1 Gain CMA (+/-)	CDKN2A Loss ^d Median ddPCR (++/+/-)	CDKN2A Loss CMA (++/+/-)
1	Metastatic	2.12 (-)	(-)	1.65 (-)	(-)	2.12 (-)	(-)	1.99 (-)	(-)
2	Borderline	2.13 (-)	(-)	1.38 (-)	(-)	1.97 (-)	(-)	1.84 (-)	(-)
3	Borderline	2.30 (-)	(-)	1.70 (-)	(-)	1.89 (-)	(-)	2.25 (-)	(-)
4	Borderline	2.59 (-)	(-)	1.52 (-)	(-)	2.15 (-)	(-)	2.18 (-)	(-)
5	Borderline	2.16 (-)	(-)	1.59 (-)	(-)	1.92 (-)	(-)	1.91 (-)	(-)
6	Benign	2.28 (-)	(-)	1.23 (-)	(-)	1.77 (-)	(-)	1.79 (-)	(-)
7	Borderline	2.14 (-)	(-)	1.37 (-)	(-)	1.89 (-)	(-)	1.86 (-)	(-)
8	Borderline	2.36 (-)	(-)	1.50 (-)	(-)	1.84 (-)	(-)	2.07 (-)	(-)
9	Benign	2.27 (-)	(-)	2.31 (-)	(-)	2.00 (-)	(-)	2.19 (-)	(-)
10	Benign	2.37 (-)	(-)	1.39 (-)	(-)	2.09 (-)	(-)	1.86 (-)	(-)
11	Melanoma	2.44 (-)	(-)	1.56 (-)	(-)	2.10 (-)	(-)	2.33 (-)	(-)
12	Melanoma	2.16 (-)	(-)	1.28 (-)	(-)	2.02 (-)	(-)	2.05 (-)	(-)
13	Borderline	2.03 (-)	(-)	1.37 (-)	(-)	1.83 (-)	(-)	1.92 (-)	(-)
14	Borderline	2.60 (-)	(-)	1.24 (-)	(-)	1.85 (-)	(-)	1.56 (+)	(-)
15	Melanoma	1.76 (-)	(-)	2.08 (-)	(-)	1.87 (-)	(-)	1.84 (-)	(-)
16	Melanoma	1.82 (-)	(-)	2.11 (-)	(-)	1.88 (-)	(-)	2.00 (-)	(-)
17	Melanoma	2.15 (-)	(-)	1.41 (-)	(-)	2.09 (-)	(-)	2.05 (-)	(-)
18	Melanoma	2.19 (-)	(-)	1.28 (-)	(-)	1.95 (-)	(-)	1.88 (-)	(-)
19	Metastatic	2.29 (-)	(-)	1.74 (-)	(-)	2.26 (-)	(+)	1.43 (+)	(+)
20	Metastatic	2.53 (-)	(-)	0.87 (+)	(+)	3.66 (+)	(+)	2.09 (-)	(-)
21	Metastatic	2.85 (+)	(+)	1.61 (-)	(-)	3.21 (+)	(+)	2.13 (-)	(-)
22	Metastatic	2.81 (+)	(+)	1.86 (-)	(-)	3.04 (+)	(+)	2.17 (-)	(-)
23	Metastatic	2.34 (-)	(-)	1.55 (-)	(-)	2.80 (+)	(+)	1.51 (+)	(+)
24	Metastatic	2.59 (-)	(+)	1.42 (-)	(-)	3.22 (+)	(+)	2.04 (-)	(-)
25	Metastatic	2.36 (-)	(+)	1.66 (-)	(-)	3.73 (+)	(+)	2.21 (-)	(-)
26	Metastatic	2.33 (-)	(+)	1.71 (-)	(-)	2.72 (+)	(+)	2.30 (-)	(-)
27	Melanoma	2.06 (-)	(-)	1.36 (-)	(+)	2.55 (+)	(+)	1.05 (++)	(++)
28	Melanoma	2.93 (+)	(+)	1.45 (-)	(-)	2.98 (+)	(+)	2.25 (-)	(-)
29	Melanoma	2.19 (-)	(-)	1.63 (-)	(-)	1.79 (-)	(-)	1.86 (-)	(+)
30	Borderline	2.32 (-)	(-)	1.45 (-)	(-)	1.85 (-)	(-)	1.54 (+)	(+)
31	Borderline	2.33 (-)	(-)	1.21 (-)	(-)	2.63 (+)	(-)	1.53 (+)	(+)
32	Borderline	2.08 (-)	(-)	1.54 (-)	(-)	1.77 (-)	(-)	1.54 (+)	(+)
33	Melanoma	3.22 (+)	(+)	0.93 (+)	(+)	2.36 (+)	(-)	2.07 (-)	(-)
34	Metastatic	4.01 (+)	(+)	0.93 (+)	(+)	3.21 (+)	(+)	1.44 (+)	(+)
35	Metastatic	3.12 (+)	(+)	1.37 (-)	(-)	2.86 (+)	(+)	1.88 (-)	(-)
36	Metastatic	3.03 (+)	(+)	1.33 (-)	(-)	2.80 (+)	(+)	2.03 (-)	(-)
37	Metastatic	5.91 (+)	(+)	1.73 (-)	(-)	2.02 (-)	(-)	1.32 (+)	(+)

38	Metastatic	5.64 (+)	(+)	1.70 (-)	(-)	1.98 (-)	(-)	1.44 (+)	(+)
39	Metastatic	2.30 (-)	(-)	1.06 (+)	(+)	1.96 (-)	(-)	0.37 (++)	(++)
40	Metastatic	2.22 (-)	(-)	1.09 (+)	(+)	1.99 (-)	(-)	0.59 (++)	(++)
41	Metastatic	2.23 (-)	(-)	1.04 (+)	(+)	1.83 (-)	(-)	0.63 (++)	(++)
42	Melanoma	2.01 (-)	(-)	1.30 (-)	(-)	3.20 (+)	(+)	1.38 (+)	(+)
43	Melanoma	1.67 (-)	(-)	0.74 (+)	(+)	2.35 (-)	(+)	1.15 (+)	(+)
44	Melanoma	2.00 (-)	(-)	0.85 (+)	(+)	2.52 (+)	(+)	0.47 (++)	(++)
45	Melanoma	2.36 (-)	(-)	0.94 (+)	(+)	3.47 (+)	(+)	0.37 (++)	(++)
46	Melanoma	3.03 (+)	(+)	2.23 (-)	(-)	3.63 (+)	(+)	0.82 (++)	(++)
47	Melanoma	2.59 (-)	(-)	1.66 (-)	(-)	1.79 (-)	(-)	1.05 (++)	(++)
48	Melanoma	2.54 (-)	(+)	1.59 (-)	(-)	2.17 (-)	(+)	1.71 (-)	(-)
49	Melanoma	2.49 (-)	(-)	1.55 (-)	(-)	2.38 (+)	(+)	2.03 (-)	(-)
50	Melanoma	2.07 (-)	(-)	1.30 (-)	(-)	2.57 (+)	(+)	2.14 (-)	(-)
51	Melanoma	2.19 (-)	(-)	1.57 (-)	(-)	2.20 (-)	(-)	1.80 (-)	(+)
52	Melanoma	1.94 (-)	(-)	1.42 (-)	(-)	2.21 (-)	(-)	1.79 (-)	(+)
53	Melanoma	2.08 (+)	(+)	1.70 (-)	(-)	3.08 (+)	(+)	0.83 (++)	(++)
54	Melanoma	2.42 (-)	(-)	1.95 (-)	(-)	2.73 (+)	(+)	2.26 (-)	(-)
55	Melanoma	2.74 (+)	(+)	1.39 (-)	(+)	2.87 (+)	(+)	2.13 (-)	(-)
56	Melanoma	3.16 (+)	(+)	1.94 (-)	(-)	2.97 (+)	(+)	1.93 (-)	(+)
57	Melanoma	2.56 (-)	(-)	1.81 (-)	(-)	2.57 (+)	(+)	1.95 (-)	(-)
58	Melanoma	2.13 (-)	(-)	2.74 (-)	(-)	3.17 (+)	(+)	2.41 (-)	(-)
59	Melanoma	1.99 (-)	(-)	2.01 (-)	(-)	1.97 (-)	(-)	1.50 (+)	(+)
60	Melanoma	2.23 (-)	(-)	2.31 (-)	(-)	2.04 (-)	(-)	0.93 (++)	(++)
61	Melanoma	2.22 (-)	(-)	2.15 (-)	(-)	2.34 (-)	(-)	0.36 (++)	(++)
62	Melanoma	3.38 (+)	(+)	2.20 (-)	(-)	2.35 (-)	(-)	1.21 (+)	(+)
63	Melanoma	4.24 (+)	(+)	1.17 (+)	(+)	2.59 (+)	(+)	3.18 (-)	(-)
64	Melanoma	2.81 (+)	(+)	1.27 (-)	(-)	2.19 (-)	(-)	0.66 (++)	(++)
65	Metastatic	2.34 (-)	(-)	1.55 (-)	(+)	2.86 (+)	(+)	1.56 (+)	(+)

Note: “ddPCR” = Droplet digital PCR; “CMA” = chromosomal microarray analysis; “Benign” = benign nevus (n=3); “Borderline” = borderline lesion (n=11); “Primary” = primary melanoma (n=33); “Metastatic” = metastatic melanoma (n=18); “ID” = case identification number; “RREBI” = Ras-responsive binding element protein 1; “CDKN2A” = cyclin-dependent kinase inhibitor 2A. Cases for which ddPCR and CMA had discordant results are bolded. The following median ddPCR cutoff values were used, per receiver operator characteristic (ROC) curve analysis:

- ^aMYC Gain
 - Median ddPCR > 2.67 = MYC Gain (+)
 - Median ddPCR ≤ 2.67 = No MYC Gain (-)
- ^bMYB Loss
 - Median ddPCR > 1.17 = No MYB Loss (-)
 - Median ddPCR ≤ 1.17 = MYB Loss (+)
- ^cRREBI Gain
 - Median ddPCR > 2.36 = RREBI Gain (+)

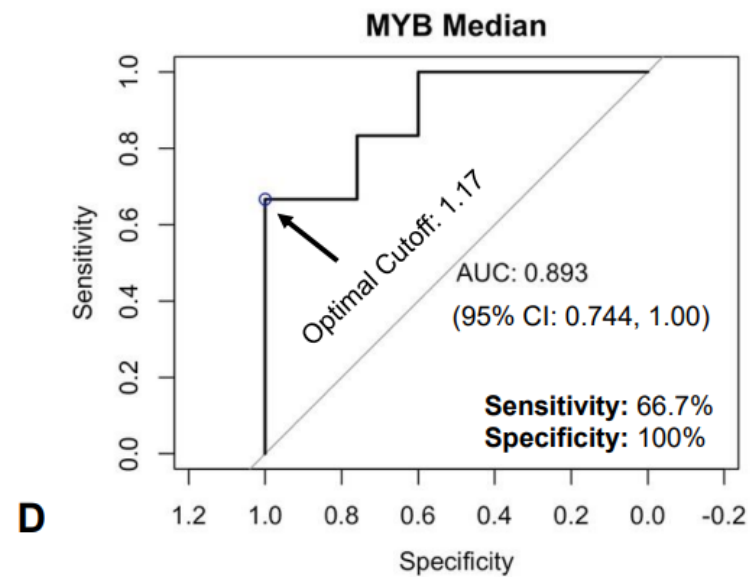
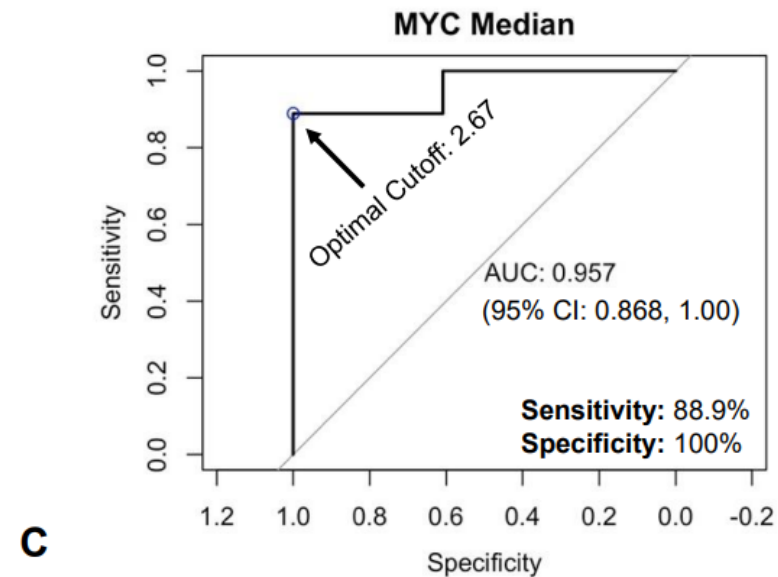
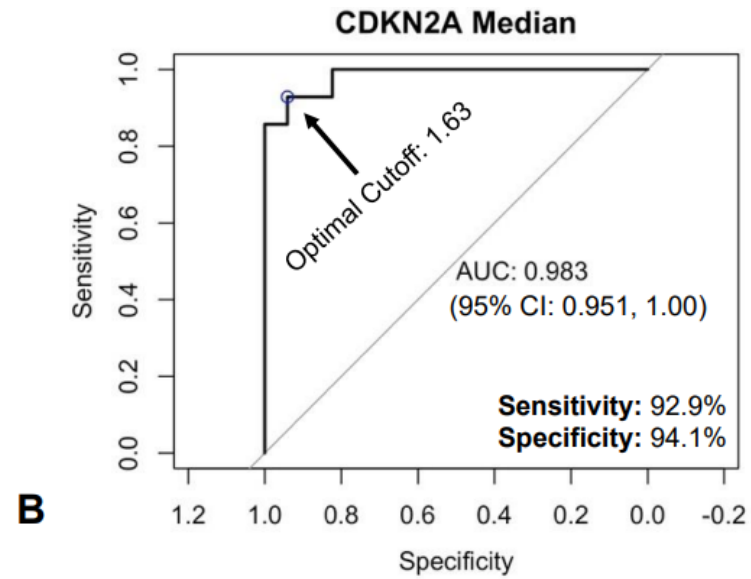
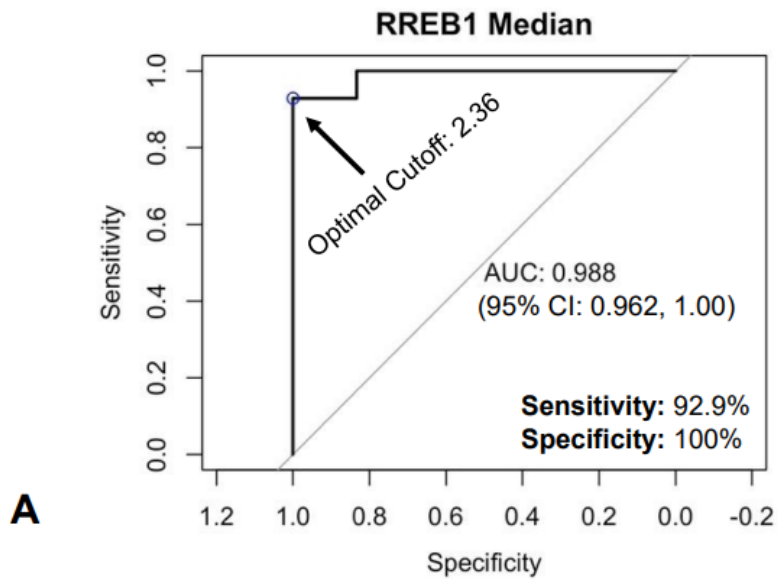
- Median ddPCR ≤ 2.36 = No *RREB1* Gain (-)
- ^d*CDKN2A* Loss
 - Median ddPCR > 1.63 = No *CDKN2A* Loss (-)
 - $1.05 < \text{Median ddPCR} \leq 1.63$ = Monoallelic *CDKN2A* Loss (+)
 - Median ddPCR ≤ 1.05 = Biallelic *CDKN2A* Loss (++)

Supplemental Table 5: Correlations with Histology

Histologic Feature	RREB1 Gain			MYB Loss			MYC Gain			CDKN2A Loss		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Lymph node-like inflammation	2.86	(.54, 19.6)	<i>P</i> = .17	1.00	(.09, 6.27)	<i>P</i> > .99	1.29	(.19, 7.05)	<i>P</i> = .71	.29	(.027, 1.72)	<i>P</i> = .16
Prominent background nevus	.58	(.086, 3.09)	<i>P</i> = .72	1.00	(.09, 6.27)	<i>P</i> > .99	.68	(.063, 4.14)	<i>P</i> > .99	.93	(.17, 4.85)	<i>P</i> > .99
Expansile, nodular growth	2.91	(.94, 9.44)	<i>P</i> = .045	2.57	(.66, 11.3)	<i>P</i> = .14	6.77	(1.74, 33.3)	<i>P</i> = .002	1.97	(.65, 6.14)	<i>P</i> = .21
Sheetlike growth	2.95	(.86, 1.8)	<i>P</i> = .06	4.47	(1.10, 19.5)	<i>P</i> = .02	6.98	(1.84, 29.3)	<i>P</i> = .002	1.08	(.32, 3.63)	<i>P</i> > .99
Epithelioid cells with abundant cytoplasm	1.38	(.42, 4.60)	<i>P</i> = .59	4.01	(.99, 17.3)	<i>P</i> = .047	6.06	(1.63, 24.7)	<i>P</i> = .003	3.07	(.91, 11.2)	<i>P</i> = .06
Necrosis	8.89	(2.43, 38.7)	<i>P</i> < .001	2.24	(.56, 9.02)	<i>P</i> = .21	4.72	(1.31, 18.4)	<i>P</i> = .009	.73	(.22, 2.33)	<i>P</i> = .60
Hemorrhage	1.59	(.42, 6.09)	<i>P</i> = .55	1.37	(.26, 6.07)	<i>P</i> = .73	1.98	(.47, 7.87)	<i>P</i> = .33	1.03	(.27, 3.86)	<i>P</i> > .99

Note: “RREB1” = Ras-responsive element binding protein 1; “CDKN2A” = cyclin-dependent kinase inhibitor 2A; OR = odds ratio; CI = confidence interval; bolding in the “P-value” column indicates statistical significance at *P* < .05.

Supplemental Figure 1: Training Cohort Results from Receiver Operator Characteristic (ROC) Curve Analysis. Data obtained from training cohorts including the ROC curves, sensitivity, and specificity of Ras-Responsive binding element protein 1 (*RREB1*) gain (A), cyclin-dependent kinase inhibitor 2A (*CDKN2A*) loss (B), *MYC* gain (C), and *MYB* loss (D), are shown. Note: “AUC” = area under the ROC curve; “CI” = confidence interval.



Supplemental Figure 2: Example of Histopathology and CMA Data for a Case with *MYB* Loss. (A) (H&E, $\times 100$): Case 44 - Photomicrograph of a melanoma with *MYB* loss. In this advanced tumor, there is a sheetlike pattern of growth, typical of cases with *MYB* loss in our series. (B) *MYB* results by ddPCR, reflecting clear separation of droplet populations, yielding a *MYB* median copy number of 0.8, with *AGO1*, *THNSL2*, *SLAIN2*, *LIPI*, *RPPH1*, *RPLPO*, *RPP30*, *MRPS30*, and *EFTUD2* as the reference genes. (C) *MYB* results by CMA, reflecting a loss of the 6q23 locus, including *MYB*.

Note: “H&E” = hematoxylin and eosin; “*AGO1*” = Argonaute RNA-induced silencing complex (RISC) catalytic component 1; “*THNSL2*” = threonine synthase like 2; “*RPPH1*” = ribonuclease P RNA component H1; “*SLAIN2*” = SLAIN Motif Family Member 2; “*EFTUD2*” = Elongation Factor Tu GTP Binding Domain Containing 2; “*RPLPO*” = Ribosomal Protein Lateral Stalk Subunit P0; “*MRPS30*” = mitochondrial ribosomal protein S30; “*RPP30*” = Ribonuclease P/MRP Subunit P30.

