

1 **Supplemental Table S1. Tumour characteristics**

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Sample	Gender	Age	Follow up (months)	Outcome	Treatment	DSM	cg11850659 methylation	cg01149192 methylation	Biomarker Outcome
1	M	66	59	NR	BCG 6+3		41	61	True Negative
2	M	84	28	NR	Nil		54	74	True Negative
3	M	59		NR	Nil		32	66	True Negative
4	M	80		NR	BCG 6+3+18		86	61	True Negative
5	M	64	54	NR	BCG 6+2+3		36	40	True Negative
6	M	78	48	NR	BCG 6+3+6		25	31	True Negative
7	M	69	40	NR	BCG 6		26	92	True Negative
8	F	71	66	R	BCG 6+3+15		76	36	True Positive
9	F	87	15	R	Nil	x	57	10	True Positive
10	F	83	52	R	BCG 6+3		67	25	True Positive
11	M	87	60	R	-		66	28	True Positive
12	M	70	48	R	BCG 6+3+9		97	11	True Positive
13	M	67	40	R	BCG 6+3+3		55	13	True Positive
14	M	92	17	R	Nil		68	65	False Negative
15	F	65	6	P	Nil	x	93	10	True Positive
16	M	68	21	P	BCG 6	x	61	9	True Positive
17	M	72	6	P	BCG 6+3		98	11	True Positive
18	M	45	22	P	BCG 6+3		46	23	False Negative
19	M	60	28	P	Nil		53	21	True Positive
20	M	75	17	P	BCG 6+2	x	87	11	True Positive
21	F	84	10	P	BCG 6+3	x	54	11	True Positive
22	M	79	32	NR	BCG 6+3		73	8	False Positive
23	M	72	68	NR	BCG 6+3+6		23	19	True Negative
24	M	77	48	NR	Nil		68	52	True Negative
25	F	77	66	NR	BCG 6+3		75	48	True Negative
26	M	70	73	NR	BCG 6+2		55	16	False Positive
27	F	69	66	NR	BCG 6+3		61	7	False Positive
28	M	80	15	NR	BCG 6+6	x	89	5	False Positive
29	M	48	64	NR	BCG 6		43	62	True Negative
30	M	71	45	NR	BCG 6+3	x	74	53	True Negative
31	M	81	60	NR	BCG 6		83	55	True Negative
32	F	69	52	NR	BCG 6+3		21	11	True Negative
33	M	75	53	NR	BCG 6+3		43	14	True Negative
34	M	59	50	NR	BCG 6+3		42	68	True Negative
35	F	68	30	NR	BCG 6+3		82	5	False Positive
36	M	62	19	NR	BCG 6+3+3	x	49	46	True Negative
37	M	86	52	NR	BCG 6		51	7	True Negative
38	F	78	75	NR	BCG 3		47	81	True Negative
39	M	77	60	R	BCG 6		56	39	True Positive
40	M	84	44	R	BCG 6		69	37	True Positive
41	M	72	30	R	BCG 6		65	39	True Positive
42	M	79	53	R	BCG 6	x	26	11	False Negative
43	M	70	15	R	BCG 6	x	81	41	True Positive
44	F	81	14	R	BCG 6+3		74	41	True Positive
45	M	68	12	R	BCG 6+3		48	9	False Negative
46	M	79	16	R	BCG 6+3		66	8	True Positive
47	M	76	14	P	Nil	x	96	22	True Positive
48	M	79	11	P	BCG 6	x	61	32	True Positive
49	M	75	9	P	BCG 6	x	100	8	True Positive
50	M	66	1	P	BCG 6+3+3	x	78	50	True Positive
51	M	61	8	P	BCG 6+3	x	68	9	True Positive
52	F	82	3	P	BCG 6+3+1	x	44	71	False Negative
53	F	74	21	P	BCG 6+3		87	34	True Positive
P value ^a	0.452	0.840			0.230	0.108	0.088	0.048	

3 ^a P value based upon multiple regression with disease outcome (no recurrence vs recurrence/progression) as the dependent
4 variable

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6 **Supplemental Table S2. 206 differentially methylated CpGs**

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cg09964670	cg12905114	cg19803976	cg05914696	cg16761035	cg01886630	cg10209635
cg24668150	cg21518056	cg14619443	cg09121623	cg00039385	cg17274024	cg17514420
cg04856657	cg20874811	cg03547220	cg08140712	cg11332786	cg11238952	ch.1.95724F
cg24096964	cg20383084	cg13094338	cg09704885	cg19457237	cg20463312	cg03418289
cg09039698	cg25431547	cg10318510	cg22299719	cg05588334	cg18916488	cg03511402
cg17853302	cg18596683	cg25421663	cg08900101	cg15047610	cg11712793	cg11476211
cg13863009	cg06476034	cg13817083	cg00703822	cg01153979	cg20965815	cg27650554
cg22598840	cg11878675	cg27331738	cg00378142	cg13369210	cg11850659	cg24119612
cg01737828	cg00608006	cg05422394	cg22917617	cg17345036	cg08281469	cg26237168
cg25714381	cg14723014	cg20237074	cg09137124	cg23618091	cg12228319	cg17631972
cg05202407	cg18167329	cg13999143	cg20181426	cg25770096	cg17297696	cg15785720
cg18364820	cg15264255	cg04933640	cg08175854	cg22829182	cg22040989	cg06948408
cg24251339	cg01823238	cg23242708	cg04622480	cg12646585	cg10321928	cg00730653
cg14279007	cg04001090	cg04265957	cg00329052	cg02787767	cg12251508	cg21912093
cg02784812	cg12741710	cg18519450	cg13703859	cg25492195	cg17180705	cg26706201
cg15898026	cg04826422	cg08274876	cg20120351	cg11664825	cg21116447	cg05382730
cg14108492	cg15676241	cg17438155	cg15992843	cg02578312	cg23174932	cg26102512
cg12175172	cg03369671	cg25373794	cg13322920	cg22328426	cg27084746	cg23534983
cg01970017	cg21380280	cg10132157	cg22428762	cg15632826	cg22753340	cg19049607
cg08652337	cg06471681	cg17398312	cg00089695	cg14552801	cg01919999	cg00747184
cg17054900	cg21908259	cg21781308	cg20510207	cg12050358	cg04382470	cg19746940
cg23545105	cg23991039	cg24847601	cg07646731	cg11850468	cg00397479	cg03549244
cg09793700	cg14105047	cg11642377	cg16383222	cg10336935	cg19182537	cg04489786
cg14233644	cg14877226	cg21162029	cg17219432	cg25763542	cg19509393	cg06607594
cg26582643	cg14556515	cg04075986	cg18061847	cg04371818	cg01149192	cg13583414
cg16099036	cg13391849	cg01472026	cg06376033	cg15821544	cg12539415	cg06128043
cg03147337	cg17541922	cg04684553	cg11089837	cg02904184	cg03540028	cg25593476
cg25054052	cg07889284	cg10236245	cg00261416	cg03498697	cg14729962	cg01392017
cg20964856	cg13861342	cg12226306	cg01485009	cg04415176	cg06391663	cg06172626
cg09286253	cg19922518					

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10 **Supplemental Table S3.** Primer sequences

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CG ID	Forward Primer 5' 3'	Reverse Primer 3' 5'	Sequencing Primer	Amplicon Size
CG11850659	AGTTTTATAGTAGTAATTTGGGTGTT	TCATTTTCCCTTAAAACTCAT (biotinylated)	AGAGTTAATGTGGAGTTAT	230
CG01149192	GGTTGTTGTTATGTGATTAGGA	AACCCCTACCACCTA (biotinylated)	GGTTTTAGAGAAATAAAGG	251

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14 **Supplemental Table S4.**

15 **ROC curve**

Variable	Hyper candidate cg11850659
Classification variable	Recurrence/progression of HR-NMIBC
Area under the ROC curve (AUC)	0.711
Standard Error a	0.0742
95% Confidence interval b	0.570 to 0.827
z statistic	2.846
Significance level P (Area=0.5)	0.0044
Associated criterion	>51
Sensitivity	86.21
Specificity	54.17

16 **Criterion values and coordinates of the ROC curve**

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥21	100.00	88.1 - 100.0	0.00	0.0 - 14.2	1.00	
>25	100.00	88.1 - 100.0	12.50	2.7 - 32.4	1.14	0.00
>26	96.55	82.2 - 99.9	16.67	4.7 - 37.4	1.16	0.21
>43	96.55	82.2 - 99.9	41.67	22.1 - 63.4	1.66	0.083
>46	89.66	72.6 - 97.8	41.67	22.1 - 63.4	1.54	0.25
>47	89.66	72.6 - 97.8	45.83	25.6 - 67.2	1.66	0.23
>48	86.21	68.3 - 96.1	45.83	25.6 - 67.2	1.59	0.30
>51	86.21	68.3 - 96.1	54.17	32.8 - 74.4	1.88	0.25
>53	82.76	64.2 - 94.2	54.17	32.8 - 74.4	1.81	0.32
>54	79.31	60.3 - 92.0	58.33	36.6 - 77.9	1.90	0.35
>55	75.86	56.5 - 89.7	62.50	40.6 - 81.2	2.02	0.39
>57	68.97	49.2 - 84.7	62.50	40.6 - 81.2	1.84	0.50
>61	62.07	42.3 - 79.3	66.67	44.7 - 84.4	1.86	0.57
>67	48.28	29.4 - 67.5	66.67	44.7 - 84.4	1.45	0.78
>68	41.38	23.5 - 61.1	70.83	48.9 - 87.4	1.42	0.83
>69	37.93	20.7 - 57.7	70.83	48.9 - 87.4	1.30	0.88
>73	37.93	20.7 - 57.7	75.00	53.3 - 90.2	1.52	0.83
>74	34.48	17.9 - 54.3	79.17	57.8 - 92.9	1.66	0.83
>75	34.48	17.9 - 54.3	83.33	62.6 - 95.3	2.07	0.79
>81	24.14	10.3 - 43.5	83.33	62.6 - 95.3	1.45	0.91
>86	24.14	10.3 - 43.5	95.83	78.9 - 99.9	5.79	0.79
>87	17.24	5.8 - 35.8	95.83	78.9 - 99.9	4.14	0.86
>89	17.24	5.8 - 35.8	100.00	85.8 - 100.0		0.83
>100	0.00	0.0 - 11.9	100.00	85.8 - 100.0		1.00

18 **ROC curve**

Variable	Hypo candidate cg01149192
Classification variable	Recurrence/progression of HR-NMIBC
Area under the ROC curve (AUC)	0.644
Standard Error	0.0854
95% Confidence interval b	0.501 to 0.771
z statistic	1.690
Significance level P (Area=0.5)	0.0910
Associated criterion	≤41
Sensitivity	89.66
Specificity	54.17

19 **Criterion values and coordinates of the ROC curve**

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<5	0.00	0.0 - 11.9	100.00	85.8 - 100.0		1.00
≤7	0.00	0.0 - 11.9	83.33	62.6 - 95.3	0.00	1.20
≤8	6.90	0.8 - 22.8	79.17	57.8 - 92.9	0.33	1.18
≤10	24.14	10.3 - 43.5	79.17	57.8 - 92.9	1.16	0.96
≤11	41.38	23.5 - 61.1	75.00	53.3 - 90.2	1.66	0.78
≤13	44.83	26.4 - 64.3	75.00	53.3 - 90.2	1.79	0.74
≤19	44.83	26.4 - 64.3	62.50	40.6 - 81.2	1.20	0.88
≤28	62.07	42.3 - 79.3	62.50	40.6 - 81.2	1.66	0.61
≤31	62.07	42.3 - 79.3	58.33	36.6 - 77.9	1.49	0.65
≤39	82.76	64.2 - 94.2	58.33	36.6 - 77.9	1.99	0.30
≤40	82.76	64.2 - 94.2	54.17	32.8 - 74.4	1.81	0.32
≤41	89.66	72.6 - 97.8	54.17	32.8 - 74.4	1.96	0.19
≤48	89.66	72.6 - 97.8	45.83	25.6 - 67.2	1.66	0.23
≤50	93.10	77.2 - 99.2	45.83	25.6 - 67.2	1.72	0.15
≤62	93.10	77.2 - 99.2	20.83	7.1 - 42.2	1.18	0.33
≤65	96.55	82.2 - 99.9	20.83	7.1 - 42.2	1.22	0.17
≤68	96.55	82.2 - 99.9	12.50	2.7 - 32.4	1.10	0.28
≤71	100.00	88.1 - 100.0	12.50	2.7 - 32.4	1.14	0.00
≤92	100.00	88.1 - 100.0	0.00	0.0 - 14.2	1.00	

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Supplemental Figure S1. Flowchart of processes to identify potential predictive biomarkers.

